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The INTERNATIONAL CONFERENCE OF PHYSICIANS was held in London from September 8 to September 12. The five sessions of the section of Cardiology were attended by four or five hundred physicians among whom were welcomed many distinguished visitors from overseas. Two of the sessions were joint meetings with the section of Pædiatrics and the section of Disorders of the Chest, respectively.

THE SURGERY OF CONGENITAL HEART DISEASE

September 9, 1947. Joint Meeting with Section of Pædiatrics

MALFORMATIONS OF THE HEART AMENABLE TO THE BLALOCK-TAUSSIG OPERATION

BY HELEN B. TAUSSIG,* Baltimore, Maryland

There are three types of malformation of the heart that cause persistent cyanosis. In the first group there is lack of adequate pulmonary blood flow, as for example in pulmonary stenosis and pulmonary atresia. In the second group there is difficulty in the direction of oxygenated blood to the systemic circulation, as in complete transposition of the great vessels. In the third group there is failure of the blood to be fully oxygenated in its passage through the lungs, as in the Eisenmenger complex. It is only the first of these three groups that is amenable to the Blalock-Taussig operation, and hence only this group is discussed in this paper.

The operation developed by Dr. Alfred Blalock is designed to increase the circulation to the lungs. This is accomplished by the anastomosis of the proximal end of one of the systemic arteries to the side, or distal end, of the right or left pulmonary artery. In order that the blood should flow from a systemic artery to a pulmonary artery the pressure in the systemic circulation must be higher than that in the pulmonary circulation. This is true in all cases of pulmonary stenosis or atresia. In such malformations a Blalock-Taussig operation virtually restores the condition to that existing before the closure of the ductus arteriosus. When there is pulmonary atresia, only rarely does the collateral circulation develop with sufficient rapidity to enable the infant to survive the closure of the ductus arteriosus. Consequently, in such instances, if operation is to be life-saving, it must usually be performed before the ductus arteriosus undergoes obliteration. When, however, there is pulmonary stenosis, operation can usually be postponed until childhood.

The diagnosis of pulmonary stenosis or atresia is based upon the history, combined with certain clinical and radiological findings. The history of the development of cyanosis at an early age is a characteristic of this malformation. The position which the child assumes when tired is a diagnostic aid because most children who suffer from a reduction in pulmonary blood flow squat when tired.

The outstanding findings on physical examination are persistent cyanosis combined with a heart that is little, if at all, enlarged, a basal systolic murmur and a clear second sound. The electrocardiogram shows a right axis deviation. X-ray of the heart shows an absence of the normal pulmonary conus and upon fluoroscopy there is absence of pulsations of the hilar shadows.

The degree of cyanosis is subject to great variation. Most children are intensely cyanotic. There are, however, a few with a tetralogy of Fallot but with lips

* From the Department of Pædiatrics of the Johns Hopkins University and the Cardiac Clinic of the Harriet Lane Home of the Johns Hopkins Hospital.

of normal colour and only slight cyanosis of the fingernails, who are extremely incapacitated. Upon exercise such children usually suffer from a marked fall in the oxygen saturation of the arterial blood.

The cardiac findings are also variable. A basal systolic murmur and a clear second sound are the rule. However, with extreme pulmonary stenosis there may be no murmur. Usually diastole is clear.

The exact diagnosis of the anatomical abnormality is not as important as it is to have the malformation amenable to surgery. The essential criteria for successful operation are: (1) the lack of adequate circulation to the lungs; (2) the availability of a systemic artery; (3) the existence of a pulmonary artery; (4) a pressure greater in the systemic than in the pulmonary artery; (5) the structure of the lungs such that the patient can survive the collapse of one lung and the occlusion of one pulmonary artery; and (6) a heart of such size and structure that it can adjust to the altered circulation.*

Although the existence of a pulmonary artery and of low pulmonary pressure are essential for successful operation, these facts are not always easy to determine prior to operation.

Fluoroscopy is of prime importance both for the visualization of the pulmonary artery and for determining the presence or absence of hilar pulsations. In infants who suffer from lack of adequate pulmonary blood flow, the lungs are usually exceptionally clear. In adults with a large pulmonary artery and high pulmonary pressure, the visualization of hilar pulsations when present is usually not difficult. In children, however, the vessels are smaller and the pulsations are correspondingly more difficult to see. In the rare instances of complete transposition of the great vessels, the pulmonary artery lies posterior to the aorta and there is a considerable amount of lung tissue overlying the pulmonary artery. Under such circumstances the pulsations in the pulmonary artery are difficult, if not impossible, to demonstrate.

Furthermore, the hilar shadows increase as the collateral circulation develops through the posterior mediastinal vessels. These shadows are caused by an aggregation of small vessels and when the observer's eyes are fully dilated appear as an aggregation of minute shadows, which never show expansile pulsations. Absence of hilar pulsations is a pre-requisite for the operation, as their presence is a strong indication of adequate or excessive pulmonary blood flow and is usually indicative of high pulmonary pressure. Nevertheless, in the absence of hilar pulsations, the existence of a pulmonary artery cannot be determined with certainty prior to operation.

The occurrence of a continuous murmur calls for careful consideration. Such a murmur may be caused by the persistent patency of the ductus arteriosus or by the flow of blood through large vessels of the collateral circulation. The differentiation is important because in the former condition there is certainly a pulmonary artery and therefore operation is possible; whereas in the latter there may be no pulmonary artery in which case operation will be impossible.

As regards the size and structure of the heart, great cardiac enlargement is a contraindication for operation because should the operation cause further enlargement the patient would be unable to maintain compensation.

An over-riding aorta or some pathway for the direction of venous blood into the systemic circulation is essential because it is the direction of venous blood to the lungs that is of benefit to the patient. Indeed, the fundamental difference between the artificial ductus arteriosus in a tetralogy of Fallot and an uncomplicated ductus arteriosus or an arteriovenous aneurysm is that in the former the dextroposed aorta permits the direction of mixed venous blood to the lungs; whereas in the latter conditions only fully oxygenated blood is redirected to the lungs. In a patient with a tetralogy of Fallot, although operation may lead to a marked rise in the oxygen saturation of the arterial blood, the oxygen content of the arterial blood never reaches normal because of the over-riding of the aorta. The saturation of the arterial blood remains between 75 and 85 per cent, and upon exercise it drops to 70 per cent or less. Consequently the blood directed through the artificial pathway to the lungs is essentially that normally directed through the pulmonary artery to the lungs.

The simplest method for the demonstration of the dextroposition of the aorta is by the determination of the circulation time. A short circulation time, arm to tongue, of less than 10 seconds is strong presumptive evidence that venous blood is being pumped directly into the systemic circulation. In doubtful cases, angiocardiography may be necessary to determine the time at which the aorta is visualized.

Cardiac arrythmias are dangerous. Partial heart block of such a nature that the heart slows with exercise is especially dangerous, because at the end of the operation the heart normally accelerates to adjust to the increased pulmonary blood flow. Slowing of the heart rate at this time is liable to lead to acute cardiac dilatation and standstill.

* These criteria were discussed in detail in the Brown Memorial Lecture given by the author in Atlantic City, June 1947, entitled "An Analysis of Malformations of the Heart Amenable to a Blalock-Taussig Operation," to be published in the *American Heart Journal*.

Rotation of the heart upon its axis calls for careful investigation, as this condition is frequently associated with a complicated malformation.

The over-all mortality rate of the first 350 patients* submitted to a Blalock-Taussig operation is shown in Table I. Although not shown in this table, the mortality rate in infants and in adults has been considerably higher than in children. The mortality rate in infants has been approximately 30 per cent and that in children approximately 10 per cent and in adults approximately 18 per cent. The 16 instances in which only exploratory operation was performed include patients in whom no pulmonary artery was found, patients in whom the pulmonary pressure was abnormally high, and patients in whom the heart action was so poor that Dr. Blalock was forced to close the chest even though the condition appeared to be amenable to surgery. The eight cases (or 2·5 per cent) in which there was no improvement indicate how seldom a thrombosis occurred at the site of the anastomosis.

TABLE I

RESULTS OF THE FIRST 350 BLALOCK-TAUSSIG OPERATIONS

	Total No. of Cases	Percentage
Deaths	60	17·0
Exploratory	16	4·5
Unimproved	8	2·5
Slight improvement	18	5·0
Excellent	248	71·0

The amount of the benefit derived from operation depends upon the size of vessel used for the anastomosis, the extent of the over-riding of the aorta, and the existence of other malformations in addition to a tetralogy of Fallot. The beneficial effects of operation are measured by the changes in the blood, by the changes in the heart size, and by the increase in the exercise tolerance of the individual. The oxygen saturation of the arterial blood rises to between 75 and 90 per cent and the red blood cell count, the hemoglobin level, and the hematocrit reading return to normal values.

The changes in the oxygen saturation of the arterial blood in four typical cases are shown in Table II. The first column gives the pre-operative values; the second column shows the rise in the oxygen saturation approximately three weeks after operation; the subsequent columns give the values at six months, one year, and two years after operation. In Case 2 it will be noted that the oxygen saturation after two years had fallen. Table III gives the red blood cell counts and the hematocrit values on the corresponding patients at the corresponding times. In these tables it is seen that in Case 2 the fall in the oxygen saturation was not accompanied by a rise in the red blood cell count or in the hemoglobin level; therefore the lower oxygen saturation of the arterial blood was probably due to the fact that the child was crying (not in a basal state) when the sample was taken. As shown in these tables, in most instances after operation the oxygen saturation of the arterial blood rises to between 75 and 85 per cent and the red blood cell count, the level of the available hemoglobin and the hematocrit reading return to normal values.

Case 4 is from the record of an infant, and as so frequently happens in spite of extreme anoxæmia, he did not have polycythemia. In this instance the oxygen saturation of the arterial blood has risen steadily but has not yet reached the optimum level,

TABLE II

THE PERCENTAGE OF OXYGEN SATURATION OF THE ARTERIAL BLOOD BEFORE AND AFTER A BLALOCK-TAUSSIG OPERATION

	Name	Before oper.	After operation			
			Immed.	6 mo.	1 yr.	2 yr.
1.	R. S.	78·0	85·0	86·9	88·4	88·4
2.	J. S.	65·8	79·5	84·0	83·0	68·0
3.	H. C.	65·9	81·4	82·0	—	83·0
4.	M. C.	20·6	47·9	58·9	59·0	64·0

TABLE III

RED BLOOD CELL COUNT IN MILLIONS AND HEMATOCRIT READING IN FOUR CASES OF A TETRALOGY OF FALLOT BEFORE AND AFTER A BLALOCK-TAUSSIG OPERATION

	Name	Before oper.	After operation			
			Immed.	6 mo.	1 yr.	2 yr.
			Red cell count			
1.	R. S.	6·4	5·5	5·5	5·5	5·5
2.	J. S.	9·0	6·9	5·3	5·0	4·8
3.	H. C.	10·5	6·6	5·5	—	5·5
4.	M. C.	5·7	5·2	6·3	6·3	6·4
			Hematocrit			
1.	R. S.	59	48	42	46	47
2.	J. S.	71	56	44	47	41
3.	H. C.	86	57	48	—	47
4.	M. C.	48	43	48	47	53

* Since the paper was read, Dr. Blalock and his assistants have operated on more than 250 additional patients with an operative mortality rate of less than 10 per cent.

and the red blood cell count and the hematocrit value have also risen. It is to be hoped that when the oxygen saturation of the arterial blood reaches 75 per cent, the red blood cell count and hematocrit reading will again decline.

In every instance the above changes are accompanied by a dramatic change in the patient's physical condition. The lips are usually of normal colour and although the fingernails may show a tinge of cyanosis, the clubbing slowly recedes; furthermore the patient's exercise tolerance is greatly improved.

The ability of the heart to adjust to the operation is shown by the after course. The degree of cardiac enlargement has varied from patient to patient, and by and large it has varied with the size of the vessel anastomosed to the pulmonary artery. In most instances, however, the heart has been able to adjust to the load and to maintain compensation. Indeed, only 3 of the first 220 patients, operated on for pulmonary stenosis or atresia and discharged improved, have subsequently died of cardiac failure. Two of these three were known not to have a tetralogy of Fallot because they both showed electrocardiographic evidence of a left axis deviation. Two other patients have developed cardiac failure and, in addition, two children have shown radiological evidence of progressive cardiac enlargement. That progressive cardiac enlargement and cardiac failure are the exception, not the rule, is shown by the fact that approximately 30 per cent of the patients have shown no change in the size of the heart following operation; 30 per cent have shown an increase in size during the first three weeks after operation and thereafter have shown no further increase in heart size; and approximately 30 per cent have shown an increase in heart size between the time of discharge and their return for the six months checkup and thereafter have shown no further cardiac enlargement.

All patients are permitted full activity at the end of the third month after operation. The extent of the improvement in the exercise tolerance has been tremendous. We expect any child with a pulmonary stenosis or atresia to walk more than a mile after a successful operation. Many a child three months after has walked six miles, and more than one twelve-year old boy who estimated his exercise tolerance before operation as three or four city blocks has been on a 10-mile hike within the first six months after operation.

Surgical Treatment of Pulmonic Stenosis

By Alfred Blalock, Baltimore, Maryland

I wish to thank the members of the Section of Cardiology for the privilege of participating in this symposium.

Six years ago Dr. Edwards A. Park and I carried out experiments in an attempt to devise a treatment for coarctation of the aorta. The thoracic aorta of the experimental animal was cut across, the two ends were closed and the subclavian artery was used to by-pass the point of occlusion. Before this method was used in the treatment of coarctation in man, a better method was developed by Dr. Crafoord of Stockholm: his operation is the preferred procedure but there are some instances in which it is necessary to employ the method which Dr. Park and I described.

In discussing the experimental work on coarctation with Dr. Helen Taussig, she suggested that I try to find a method for increasing the blood flow to the lungs in cyanotic patients with pulmonic stenosis. As you know, the most common abnormality of this type is the tetralogy of Fallot. This problem was investigated in the experimental laboratory and I found that the cyanosis produced by an operative procedure which I shall not go into at this time could be partially alleviated by the creation of an artificial ductus. After the experimental work was completed, the problem was returned to the clinic and work on patients was begun.

As Dr. Taussig has said, the major difficulty in the tetralogy of Fallot is the pulmonic stenosis. Fortunately the stenosis is usually limited to a single point (pulmonary conus region), and the pulmonary artery distal to this point is usually a fair sized vessel. Since this is true, the pulmonary artery in most cases is suitable for anastomotic purposes.

I would like to review for a moment the anatomy of this region. As you know, the arch of the aorta usually gives rise to the innominate artery, the left carotid artery, and the left subclavian artery. When the aortic arch descends to the left, which is usually the case, the innominate arises on the right side. When the aortic arch descends to the right, which is observed in one-fourth of our cyanotic patients, the innominate arises on the left. I prefer to use the subclavian branch of the innominate for the anastomosis, and hence the position of the aorta should be determined pre-operatively. This can be done with great accuracy by the use of the method of Bedford and Parkinson of London. The incision is usually made on the side opposite that on which the aorta descends. The operative procedure consists of anastomosing a branch of the

aorta or the aorta itself (as recommended recently by Potts) to one of the two pulmonary arteries. As you know, the pressure in the pulmonary artery is low, the pressure in the aorta and its branches is high, and a large quantity of blood will flow from the systemic to the pulmonary circuit after such an anastomosis is made. The incision is made with the patient lying on his back but with the side to be operated upon at a slightly higher level. This leaves the opposite lung in good condition for carrying out respiratory functions during the operative procedure. After the pleural cavity has been entered, the azygos vein is doubly ligated and divided. The pulmonary artery is then exposed and it is dissected free of the surrounding tissues. The innominate with its branches is then exposed and in the usual operation the subclavian branch of the innominate is ligated distally. It is occluded proximally with a bulldog clamp and is cut across proximal to the ligature. The pulmonary artery is then occluded proximally with a special rubber-shod instrument and distally with a bulldog clamp, and a transverse opening is made on its upper surface between the two points of occlusion. Using fine non-absorbable suture material an anastomosis is then made between the end of the subclavian and the side of the pulmonary artery. The subclavian branch of the innominate makes a good angle with its parent vessel and stenosis at the point of origin is not nearly so apt to occur as when the subclavian artery that arises directly from the aorta is used.

As stated previously, the end-to-side type of anastomosis is preferred. In some instances, however, it is necessary to do an end-to-end anastomosis after having ligated and divided one of the pulmonary arteries. One of the advantages of the end-to-side anastomosis is that it allows the shunted blood to go to both lungs.

The motion picture, a portion of which I will show now, illustrates the operation on a five-year-old boy who had a moderate degree of cyanosis. His disability was fairly marked. The anæsthetic agent in this case was cyclopropane with a high concentration of oxygen. The exposure of the right pulmonary artery is shown. The pressure in the artery was measured by the use of a needle and a manometer. In this patient the pressure was about 200 mm. of water (15 mm. Hg.) which is about the average pressure that we have obtained in our cases. If the pressure is higher than 375 mm. of water, we hesitate to carry out the procedure.

You will note in the picture that there is no difficulty in this case in approximating the subclavian artery to the pulmonary artery. Difficulty is encountered in some of the older, larger patients in approximating these vessels. In some of these the incision is made on the opposite side and the subclavian branch of the aorta is used. You will note that the transverse opening in the upper surface of the pulmonary artery is slightly larger than the end of the subclavian artery. You will note also that the suture everts the intima of the vessels.

I now show you a picture of this boy 18 days after the operation. You will observe that his cyanosis is much lessened. It takes a longer period of time for the characteristic clubbing of the fingers to disappear. More important, however, is the lessening or the disappearance of the disability. Thus far some of the patients seem to be able to lead normal lives.

A few comments might be of interest regarding the various vascular anomalies we have found. In the first 475 patients there were 121 in whom the aortic arch was on the right and in the majority of these there was an obliterated ductus which joined the subclavian branch of the innominate. In at least 14 of these patients there was an anomaly in the position of the superior or inferior vena cava or both ; the number is probably considerably in excess of this. In at least 5 the superior pulmonary vein entered the superior vena cava. In 15 patients or more there was rotation of the heart to the right. Various other arterial and venous anomalies were encountered.

The mortality rate has been high but not discouragingly so. When the last analysis was made, it was found that 474 patients who were thought pre-operatively to have the tetralogy of Fallot or one of its variations had been operated upon. An end-to-side anastomosis between the subclavian artery and the pulmonary artery was performed in 331 of these and among these there were 37 deaths, or 11 per cent. Among the patients who succumbed in this group there were three with transposition of the aorta and the pulmonary artery and one with truncus arteriosus. Several of the deaths occurred a number of months following the operation.

An end-to-end anastomosis between a branch of the aorta and the divided distal end of one of the pulmonary arteries was performed in 23 cases with 4 deaths. An end-to-side anastomosis between one of the carotid arteries and a pulmonary artery was performed in 30 cases with 9 deaths. An end-to-side anastomosis between the innominate artery and a pulmonary artery was carried out in 47 cases with 13 deaths. A side-to-side anastomosis between the aorta and one of the pulmonary arteries was performed in 2 cases with 1 death. In 37 of the total number of cases only an exploratory thoracotomy was performed; in most of these a pulmonary artery was not present or at least could not be found. Among these patients who

had an exploratory thoracotomy without an anastomosis there were 18 deaths. In the entire total of 474 cases there were 86 deaths, a mortality of 18 per cent. This includes all patients who have died, whether in hospital or after leaving hospital, and whether or not an anastomosis was performed.

There has been no serious disturbance of the circulation of the arm, the subclavian of which was ligated, in any of the patients and the function of the arm is excellent. There have been approximately 400 such patients in whom the subclavian artery was ligated and divided.

The age of patients operated upon has varied from two months to 44 years. We consider the ideal age for operation to be from three to nine years. All of the patients received penicillin. There have been no instances of empyema or pericarditis. Heparin and dicumarol have been used very rarely.

In conclusion I would like to say that it is too early to evaluate the ultimate effects of this operative procedure since it has been less than three years since the first such operation was performed. We can state that the results thus far are quite encouraging.

By J. W. Brown, Grimsby

Ample justification for operation is found in the relatively bad prognosis of cyanotic congenital heart disease. Observation of over 100 cases has shown that many die before the age of three, and about a quarter of the cases survive the school age. Most of the children can be educated if given the opportunity and they should always be taught to read and write. Between 60 and 70 per cent of the cases fall into the group of the tetralogy of Fallot where pulmonary stenosis is combined with a large interventricular septal defect, an over-riding dextroposed aorta, and right ventricular hypertrophy.

Cyanosis is present and depends upon the oxygen unsaturation of the blood and the polycythæmia, which in their turn are dependent upon the degree of pulmonary stenosis and upon the amount of the pulmonary blood supply. Cyanosis may vary from day to day and definitely with the season. The factor of the over-riding aorta cannot be of enormous importance when the figures of oxygen saturation after operation are considered, but it is of importance in relation to paradoxical embolism and cerebral abscess. In this series thrombotic incidents due to polycythæmia have not been frequent. Commonly there is a basal systolic murmur and a clear second sound. Absence of a murmur does not invalidate diagnosis of the tetralogy.

Diagnosis is essentially radiological, and the picture of a small pulmonary artery with a concave pulmonary arc and absence of pulmonary congestion and of hilar pulsation are convincing. A right aortic arch is frequently present, and a cœur-en-sabot may be seen in the older children. The electrocardiogram shows a right axis, but abnormalities of the ventricular complexes and conduction defects do not appear to be so common as in auricular septal defect.

There are other conditions that may be confused with the tetralogy. Tricuspid atresia is distinguished by the presence of a left axis in the electrocardiogram, a pathognomonic finding in a cyanotic case. Transposition of the great vessels usually causes gross cardiac enlargement over a short period of time, and survival is generally short. There is a narrow vascular pedicle which broadens in the oblique view, for then the aorta comes directly in front of the pulmonary artery.

The evil prognostic signs are a rising red cell count, a high hematocrit reading, syncopal attacks, and thrombosis. Many of the cases exist rather than live in the fullest sense.

The point before us is that operation is not a cure, but a physiological adjustment that allows a greater circulation to the lungs through an artificially created ductus arteriosus. The subject still remains liable to the inherent risks of the patent ductus, and the mixed blood in his aorta is little different from venous blood. The immediate results of operation are so beneficial to the patient that we must critically study every case of cyanotic heart disease so that those types of abnormality likely to be helped by operation may be recognized Where clinical and ordinary laboratory investigation fails to make a satisfactory diagnosis, some help may be had by intracardiac catheterization and by angiocardiography.

Of the operation, one is entitled to ask at this stage whether the calibre of the anastomosis created in infancy will increase pari passu with the growth of the child. There might well be the risk of contraction and ultimate obliteration at the suture line in the same way as the small ventricular septal defect of the maladie de Roger may spontaneously close by contraction of its fibrous margins. We know too that in the cyanotic case a patent ductus fulfilling an obviously physiological purpose in shunting blood between two pressure systems may quite suddenly close and bring about the death of the patient, showing that the mere fact of a shunt does not necessarily keep open an abnormal com-

munication. The Potts operation of direct anastomosis between aorta and pulmonary artery may have something to offer in allowing the surgeon to determine the size of orifice that he may make.

If prognosis is to be the basis on which surgical treatment of congenital heart disease is to be founded, the time has come when this problem should be seriously and collectively examined. Our present ideas are based upon statistics that contain many neonatal cases. Statistics depend upon the interest shown by clinicians and pathologists, and naturally the highest incidence of congenital heart disease is in children's hospitals, rather than the general hospital. Only the interesting case is reported, and no account is taken of the living because we tend to publish only the case with post-mortem control. As an example where is the adult with patent ductus arteriosus? We certainly do not see him in our clinics. He has not been cured in childhood by the surgeon as yet. Do we fail to recognize him when he is in failure, or when he has infective endocarditis? He is not seen by the pathologist who perhaps practises section of the great vessels within the pericardium. Does the ductus after all close spontaneously in adolescence or early adult life?

Coarctation of the Aorta

By C. Crafoord, Stockholm

First of all I want to say that I feel it as a great honour that I have been invited to read this paper. We have heard an excellent review by Dr. Taussig and Dr. Blalock of the work they have done on the treatment of the blue babies. There are, however, two more congenital heart malformations that have been more closely studied than ever before because experience has shown that by surgery these two can be completely cured—patent ductus and coarctation of the aorta. I am going to deal with coarctation, which has been thoroughly studied in my hospital where the first operations for this disease were performed, and to give you only a résumé of my results in patent ductus as this is going to be covered by the following speakers.

Coarctation of the aorta was first described by Morgagni in 1760. Wadstein in 1897 collected 103 reported cases. Maud Abbott (1931) described among 1000 cases with congenital cardiovascular defects 142 cases of coarctation, which indicates that about 15 per cent of all congenital lesions in this group are coarctation.

The incidence of the adult form of this malformation is about 1 per 1500–2000 when estimated from large post-mortem series. The juvenile form has no surgical interest as these cases die very early. The adult form is usually confined to the area of the ductus arteriosus. From the United States Pearlman, when examining men between 18 to 35 years of age for army service found only 1 in about 10,000. This discrepancy depends on the fact that by rapid clinical examination quite a number of coarctation cases are never detected. Both clinical and post-mortem findings show that the incidence of this congenital lesion is much more common than was previously believed and more common among men than among women. Maud Abbott gives this proportion as 3 to 1. Among my 22 resected cases 7 were females.

Other developmental disturbances may be combined with this form of coarctation: the bifid aortic cusp, estimated by Abbott to occur in 25 per cent of the cases; secondly hypoplasia of the aortic wall, according to Abbott in 10 per cent of cases, this is naturally of surgical importance and must always be borne in mind as a pronounced hypoplasia makes a resection and suture impossible to perform; thirdly patency of the ductus arteriosus; and finally there is a small group of cases in which the points of origin of the great vessels leaving the aorta are abnormally situated, the coarctation itself may be of considerable length, and defects of the ventricular or atrial septum may be present. Some of these are of importance in diagnosis because their existence may influence the decision to operate or not.

Early atherosclerosis in arteries proximal to the narrowed segment seems to be very common. The oldest patient I have resected was 27 years of age and some have been around 20: in these cases we could find very slight or no atherosclerotic changes.

The prognosis regarding length of life is of special interest. Ask Upmark (1942) found that about 25 per cent of all cases died before they reached 20, 50 per cent before 40, and 90 per cent before 50 years of age. The commonest causes of death according to Abbott are in order of frequency: congestive heart failure, rupture of the aorta or the heart, cerebral hæmorrhage, and bacterial endocarditis.

All my coarctation cases have been studied in the heart clinic of Prof. Nylin before operation, a collaboration that I consider to be of greatest importance. Coarctation seems always to be accompanied by increased blood pressure above the level of the coarctation, and decreased pressure below. It is not known how early in infancy these changes in the blood pressure are present. In

a 3-year-old child reported by Bodlander (1946) the blood pressure was 130/60 which is to be considered as hypertension at this age; erosion of the ribs was seen in the radiographs.

We are of the opinion that a higher blood pressure in the legs than in the arms practically excludes coarctation. In our material the blood pressure has been high in the arms and low in the legs in all patients. In the two youngest, both children of 11 years of age, we found systolic blood pressures ranging in the arms in one between 150 and 190, and in the other between 140 and 150 mm.

If hypertension is present, the possibility of coarctation should always be borne in mind. The subjective symptoms resulting from the hypertension in the upper part of the body vary and may include general weakness, palpitation, vertigo, throbbing headache, and a feeling of heaviness in the head, and visual troubles.

The low blood pressure in the lower half of the body, which never occurs in hypertension from other causes, not infrequently produces vague or even quite pronounced symptoms suggestive of intermittent claudication, but may cause no symptoms at all.

The majority of patients seek medical advice because of one or more of the above symptoms. The clinical findings on examination are mainly as follows:

1. By inspection and palpation abnormal pulsation is found, both in collaterals (most often in the axillæ, the supraspinous fossæ, and close to the lower borders of one or more ribs), and also in dilated arteries in the neck and head, central to the stenosis, and finally absence of pulsations in the arteries in the legs.

2. By percussion and auscultation one finds hypertrophy of the heart mainly on the left and a harsh systolic murmur over the base of the heart also at the back especially in the interscapular area to the left. Probably the murmur originates from collaterals and not from the stenosed part of the aorta. In one case of mine, in which the stenosis was complete, this systolic murmur was present before operation and vanished afterwards, which shows that the murmur could not have been due to the stenosis itself. A systolic murmur over large collaterals can also be heard and recorded phonocardiographically.

3. *Oscillographic findings.* This examination has been used with special interest in our hospital and has been carried out with a new apparatus designed by Dr. Ejrup in the heart clinic of Prof. Nylin. The recordings can be callibrated and are thus directly comparable at different examinations. The auscultatory method is adequate in studying blood pressure changes in the arms, but in the legs it is often difficult to hear the sounds when auscultating in the popliteal fossæ. The oscillogram gives a clear and visible record of the blood pressure and pulsations in the legs even in coarctation cases, and is of great interest because, as shown by Ejrup in 1945 and 1946, there is a special reaction to exercise. If in a normal case an oscillogram is taken on the upper or the lower limbs after exercise, the blood pressure is higher and the pulsations are greater than in the oscillograms taken during the rest.

In organic obstruction of the arteries and in coarctation an " inverse reaction " with a diminished blood pressure and a decrease of pulsations appears after exercise. This reaction has been found in patients with thrombo-angiitis obliterans, severe arteriosclerosis, and arterial embolism. It is not influenced by the presence or absence of intermittent claudication. In obstruction of the arteries of the lower extremities intermittent claudication will sooner or later develop if the exercise is great enough, but the abnormality is shown by oscillography long before clinical symptoms appear.

In coarctation cases at rest the oscillographic tracings show big pulsations and an elevated blood pressure in the arms and small pulsations and low blood pressure in the legs. After work test the tracings show further increase of the pulsations and the blood pressure in the arms but in the legs a paradoxical or pathological reaction is demonstrated by either a decrease of the blood pressure and the pulsations or absence of increase in blood pressure compared with the tracings at rest.

4. *X-ray examination.* We have found (A) and (B) constant findings; (C), (D), and (E) inconstant findings.

(A) Widening of the left subclavian artery which shows up as an S-curved outline to the left of the superior mediastinum, an impression on the œsophagus, and an indentation to the left in the posterior mediastinum.

(B) Dislocation and shortness of the aortic arch with absence of the aortic knuckle.

These constant findings are easy to understand. A frontal section from a frozen body in the post-mortem room makes it easy to understand that a dilatation of this left subclavian artery will produce a convex shadow against air-containing lung and an impression on the œsophagus.

The indentation we believe is most often formed between the entrance of the subclavian artery in the aorta and the aortic wall above the coarctation, and not due to the constricted area itself. The dense fibrous tissue which can be dissected when the aorta is freed at operation often gives by itself such a shadow that the actual coarctation is difficult to

see as an indentation in the X-ray film. I have, however, a picture that shows two different indentations: one cranial formed by the subclavian artery and the aorta, and one caudal due to the coarctation itself.

(C) Erosions of the ribs.

(D) Enlargement of the left ventricle and increased curve to the right of the ascending aorta.

(E) Enlargement of the left auricle.

In experimental studies on dogs in 1935–6, I demonstrated that the flow of blood to all the organs could remain suspended for as long as 25 minutes without there being any subsequent signs of organic damage, provided an adequate flow to the brain was secured. This circulation to the brain was maintained by creating anastomosis between the carotid and jugular vessels in a dog of the same size lying beside it. On the strength of this observation I took, in certain patients with a patent ductus, the risk of placing clamp forceps on the aorta above and below the point of entry of the duct, leaving them in place during the time necessary to divide the duct and suture the aorta. In one of the patients this part of the operation took no less than 27 minutes : I was forced to it because an attempted ligature cut the ductus completely with bleeding somewhat difficult to control. In spite of this no noticeable disturbances were observed.

Because of repeated experiences of clamping of the aorta in cases suitable for division of the ductus I began in 1943 to discuss whether it might not be possible to treat congenital coarctation of the aortic isthmus by resection.

In the light of the results obtained in the experiments and of the clinical experiences it seemed that in patients with congenital isthmus stenosis, who already possessed a well-developed collateral system between the large arteries arising central to the coarctation and the arteries in the lower half of the body, the aorta could be kept closed for considerably longer than 27 minutes without danger to the patient.

As far as I had been able to ascertain at that time the only other investigator who had considered the possibility of relieving coarctation surgically was Blalock, who, however, attacked the problem from a different standpoint, having considered some form of anastomosing operation or plastic reconstruction as the only way of improving the circulation peripheral to the stricture.

I, therefore, decided that the bad prognosis of aortic coarctation was a sufficient justification for attempting surgical treatment which was tried for the first time on two cases in October, 1944.

Resection of the constricted part of the aorta was carried out and the aorta was sutured end to end with oiled silk with a technique similar to the one described by Carrell. Both cases healed and normal blood pressure conditions were re-established.

Until the end of July, 1947, 22 cases have been resected with 2 deaths, one due to hæmorrhage from a divided intercostal artery from cutting through of the central ligature, and one (about a month after the operation) due to formation of a false dissecting aneurysm from insufficiency of the aortic suture. Three more cases have been explored without any attempt at resection. In one the constriction of the aorta extended from the origin of the innominate artery to well below the left subclavian artery. In the second the aortic wall was extremely thin and hypoplastic. In the third, the oldest in my series, aged 35 years, there was extensive atherosclerosis. The two first mentioned of these cases died of post-operative complications. The first had bilateral pneumonia, insensitive to penicillin and sulphonamides; he had been treated for months before operation with a combination of penicillin up to a million unites a day and sulpha-compounds because of bacterial endocarditis and with healing of this complication. The second died from extensive uncontrollable oozing from the wound, and into the pleural cavity; he had been operated on many years before for appendicitis, that time also with severe after-bleeding from the wound. The third of these patients healed without complications.

Despite this experience I would like to stress that an ordinary exploratory thoracotomy cannot be considered more dangerous than an exploratory laparotomy and is certainly justified in a great variety of cases and also in order to determine whether or not resection can be performed in those cases of coarctation that are deemed suitable for operation.

Methods of investigations taken up since a year ago, which we hope will diminish the number of explorations in coarctation cases, are cardio-angiography and heart catheterization.

By the latter method all sorts of shunts such as ventricular or atrial defects or patent ductus can be diagnosed by taking blood samples simultaneously from different parts of the heart and a peripheral artery. Cardio-angiography I believe will be of utmost importance. By this method the site and the extent of the constriction can be determined and unnecessary explorations can be avoided; it also makes it possible to study the anatomical result of the operation.

We intend now if possible to take cardio-angiograms as a routine after our operations. In 5 of 6 cases we have found normal conditions. In the

sixth there was a small vague rounded shadow close to the aorta at the calculated site of the anastomoses indicating the possibility of formation of a small aneurysm at this point. This case will be subjected to further cardio-angiograms in order to see what happens. Clinically he is in very good condition.

As mentioned we have now resected the aorta in 22 patients. Two of these died. The 20 surviving have healed without or with minor post-operative complications of no importance to the subsequent course. They have all been followed up: in all the subjective symptoms that the patients had before the operation have vanished.

In most cases the blood pressure in the arms has returned to low normal values. In a few it is still at or slightly above the normal upper limits. In all cases the blood pressure in the legs has been elevated—in some up to 10–20 mm. higher than in the arms which is to be considered as normal: in the others up to the same or slightly below the blood pressure in the arms. All the blood pressure readings I am now discussing are at rest.

In all cases the oscillograms from the lower limbs after work have gone back to normal showing much increased oscillations and an increasing blood pressure instead of the pathological or paradoxical reaction before operation.

Cardiac tolerance tests as used by Nylin have been made in all cases. In some before operation this test has indicated a certain amount of cardiac insufficiency after work. In all when these tests were repeated after operation a normal function was found. This correlates with our finding that the cardiac volume has returned to normal in all cases with pathological findings in that respect before operation. In some cases in which the heart volume has been within calculated normal values we have, however, also found a diminution after operation.

Patent Ductus Arteriosus

I want to give a brief résumé of my results in 101 operations for patent ductus. I have done double ligature with injection of 50 per cent glucose solution as a sclerosing agent between the ligature in 69 of the cases, and in the remaining 32 I have divided the ductus. In most of these I have done a clean arterial suture of the wound both in the aorta and the pulmonary artery.

All the cases have been correctly diagnosed and there was no discussion of the certainty of the diagnosis. All had the typical continuous murmur with typical localization which could be demonstrated by auscultation and verified by phono-cardiographic registration.

In all surviving cases this murmur disappeared and has not reappeared in any case.

I have divided the 101 cases into 95 non-infected cases and 6 cases with infection of the ductus and septicæmia.

In the first group 2 cases died. The first could have been avoided. Everything was quite normal until the catheter was passed through the intratracheal tube for post-operative aspiration. It was not observed that the suction catheter practically filled the whole lumen of the small intratracheal tube, and in consequence the endobronchial pressure was rendered highly negative. The same effect was produced as was described in this country from the effect of the negative pressure wave in blast injuries. There was a sudden heart stop. The wound was immediately reopened and the heart action revived by direct heart massage. The time of complete heart arrest was, however, too long, about 5 minutes, and the patient died about 48 hours later from the result of severe cerebral anoxæmia.

In the second case there was a very marked hypoplasia of the aortic wall around the ductus. This was not observed before the ductus was divided after clamping of the aorta above and below. Because of the hypoplasia of the aortic wall it was extremely difficult to obtain a sutureline without leak and the aorta had to be clamped for a little more than 45 minutes. In this case post-operative anoxæmic damage of the spinal cord developed. Because of this and other complications the patient died three weeks after operation.

This gives a mortality of just over 2 per cent in this group, with complete healing without recurrences in the surviving cases.

In the second group of 6 cases 5 healed with no complications and 1 died. This was the first in the group before we had penicillin available in Sweden. With only sulpha-drugs it was impossible to get negative blood cultures, which we have been able to obtain in the rest of the cases before operation. This fatal case seemed to heal quite all right in the beginning. She left hospital about 6 weeks after operation with negative blood cultures, normal temperature and only slightly elevated sedimentation rate. However, she came back to hospital a couple of months afterwards with all clinical signs of a recurrence of her septicæmia and also a recurrence of her ductus arteriosus. It was difficult to declare how this recurrence might have occurred as this patient was treated with complete division of the ductus and suturing of both the aorta and the pulmonary artery. I believe that an infected hæmatoma must have formed between the pulmonary artery and the aorta and that this hæmatoma secondarily must have broken into both the pulmonary artery and the aorta. The patient was submitted to a re-operation at which was found a

big false aneurysm between the aorta and the pulmonary artery with communication between the aneurysm and both the big vessels. An attempt was made to resect the aneurysm and to close the aorta and the pulmonary artery. This was, however, technically impossible to perform. After a partial resection of the aneurysm this was sutured and the chest wound closed. The patient died shortly after the operation was finished.

Patent Ductus Arteriosus

By Rae Gilchrist, Edinburgh

Notable contributions have been made to this subject in recent years. I shall confine my remarks to the diagnosis of the *patent ductus* and the results of surgical occlusion. Nearly 70 cases have been under observation and I am greatly indebted to my surgical colleagues, Sir John Fraser and Mr. Walter Mercer, who have kindly placed their operative notes at my disposal.

In diagnosis the hallmark is the continuous murmur described by Gibson, heard best below the inner end of the left clavicle and almost invariably accompanied by an accentuated second pulmonary sound. Difficulties arise in infancy before the murmur has developed its full continuous quality, and also in later life, when, in the presence of congestive heart failure, it may at times be inaudible so that the lesion escapes clinical recognition. By the time school age is reached the murmur has usually developed its distinctive continuous quality. When the channel is large, the ductus of wide bore, 1 cm. or more in diameter, the leak from the aorta to the pulmonary artery is considerable. The physical signs are then well marked, the murmur loud and roaring, with a thrill coarse and widespread. The heart is larger than when the murmur is less intense and an isolated finding. On cardioscopy a fast, vigorous over-active heart with an increased and flicking type of pulsation in the aorta and pulmonary artery is very characteristic. In my experience the dilated left auricle and a hilar dance in the smaller vessels of the lung roots are exceptional. They do not occur in the average case, but only when the ductus is of wide bore. On the other hand, in the pulmonary artery itself the vigorous, forceful pulsation—what we call in Edinburgh a Highland fling—is very characteristic.

Bohn's exercise test in our hands has not come up to expectations. When the physical signs are doubtful in a child, that is before the Gibson murmur has developed, the response of the blood pressure to exercise has seldom been of help in reaching a diagnosis. In the majority of children the electrocardiogram is of normal form. After the age of 10 years the proportion of patients who show a minor grade of left axis deviation tends steadily to increase.

In diagnosis it is important to correlate any general septicæmic signs with the local evidence of a patent ductus, as this at once gives the clue to a bacterial infection restricted at its onset to the pulmonary artery in the immediate neighbourhood of the mouth of the ductus. In the diagnosis of the infected case there is a triad of signs that make a characteristic clinical picture: (1) local evidence of a patent ductus, often overwhelmed by the more dramatic and florid features of (2) a generalized septicæmia and later as the local vegetative process advances in the pulmonary artery, and (3) multiple lung infarcts. It is, of course, desirable to make the diagnosis of endarteritis of the pulmonary artery before infarcts, systemic or pulmonary, occur. Early ligation should be urged.

With the increasing experience of the past seven years I have little hesitation in expressing the view that on the recognition of a patent ductus in childhood, surgical closure should be recommended with few exceptions. The results obtained by closure of the channel are very good. As the ductus may on occasions close spontaneously surgery can be withheld, if the physical signs are not advanced and the heart unembarrassed, perhaps until the age of 7 or 8. After this age if the ductus remains patent the child should be sent to the thoracic surgeon, preferably before the age of 10 is reached. If the signs are gross, nutrition impaired, and the child obviously handicapped, closure of the ductus should be undertaken earlier, even by the age of 3 or 4 years. After the age of 10 the surgical technique is a trifle more hazardous and the structure less resilient and the late Mr. Tudor Edwards showed that the mortality rate for intra-thoracic interference increased with each decade. In my experience the age period 7 to 10 years is for choice the most suitable time to recommend ligation. When recognized first about the age of 20 to 30 there is less justification for recommending surgery. If the general state of health is satisfactory, the response to effort good, and the heart not enlarged, then the ductus must impose no more than a trifling burden on the circulation. In these circumstances I doubt the wisdom of recommending a major

surgical procedure. The development of a fever, or any septicæmic signs demands prompt action and every care should be taken to reduce the risk of a *Streptococcus viridans* infection so commonly derived from oral or dental infection. It is important, for instance, to recommend the administration of sulphonamides over the period of dental extractions if the risks of septicæmia are to be avoided in those known to harbour this and other congenital cardiac defects.

In the immediate post-operative care of these patients measure to reduce the tendency to massive pulmonary collapse are important. A pleural effusion should be tapped even within 24 or 48 hours of operation. Respiratory exercises should be commenced at the first opportunity. In fact it is useful to have the child taught the appropriate exercises in the days before surgery is undertaken.

The results we have obtained in Edinburgh have been very satisfactory. It is seven years since the first ligation was undertaken. Deaths have occurred from massive pulmonary collapse in two infected cases and also from mediastinal infection (before penicillin was available) in one case and from hæmorrhage in another. With the exception of three patients in whom recanalization occurred the remainder have all obtained striking benefit, more than sufficient to compensate for the bitter disappointments of our earlier experience.

Perhaps one or two case records are more instructive than a statistical analysis. All the patients improved in physical fitness and general nutrition. A decrease in the size of the heart and an improved psychological outlook are the rule. A boy, attending a special school for crippled cardiacs had his ductus ligated 3 years ago; he now plays Rugby football. Only eight months ago a boy of 13 had his ductus ligated: last week his mother sent me his headmaster's report for the term: " He is an entirely different boy since his operation. His thrust and responsiveness are much more positive and sustained. We have seen this at his cricket and at his work. He has lost his diffidence." One other exceptional patient is worthy of mention, as five years have elapsed since this boy's ductus was ligated at the age of 13: within two years he gained 43 lb. in weight and grew 8 inches in stature. Since then he has been accepted as A1 for the Army, and has won a regimental boxing competition, does a 15-mile cross-country run twice a week, and claims to have done 100 yards in 10 seconds. Surgery can save lives from invalidism and prevent premature death from infection. Closure of the ductus is a most notable advance in cardiac therapeutics.

By Holmes Sellors, London

I am confining my remarks to *patent ductus arteriosus*, the only form of congenital heart disease with which I have had much experience. Previous speakers have stressed most of the clinical and therapeutic aspects of the condition, and I want to speak of some of the most unusual features. At the outset I would like to stress the view that it should be regarded as a condition requiring surgery unless there are obvious contraindications. Even though it is less than ten years since the first ductus was tied, the minimal risk of operation in practised hands far outweighs the risks that the patient undergoes from being left alone. I have been most impressed by the results, even in patients who had practically no symptoms. Children develop quickly physically and mentally, and young adults are most emphatic in stating how well they feel after the arterio-venous shunt has been relieved.

In all I have now operated on 46 patients with this lesion, with one death. Ten of these patients had infective endocarditis, and 5 were ligated in the active phase of the disease. Since the use of penicillin, we have tended to wait until the infection has been well controlled, and to tie the ductus some weeks later.

Another 10 patients were showing signs of embarrassment with dyspnœa, considerable enlargement of the heart, and subjective symptoms.

Of the remaining 24 about half complained of some disability or limitation of activities that was cured by ligation of the ductus. The others, mainly young children, were virtually symptomless.

The diagnosis depends on a combination of the classical murmur, the low diastolic pressure, and radiography; and it is fair to say that the murmur occupies most attention. In our 46 cases the murmur and thrill could be regarded as typical in 35. But there were two patients in whom no murmur was heard until infective endocarditis developed—one of these had been fully investigated some months previously, and the evidence for previous absence in the other case was quite strong. In other words, a thrill or murmur can be absent with a patent ductus.

Next there was a group of 9 cases in which the murmur was atypical. In 5 instances a harsh systolic sound only could be detected, and in the remaining 4 the lesion was probably complicated. The diagnosis had to be based on other factors, but in each patient the patent ductus was recognized and occluded. This brings me to an important point in the observation and behaviour of the

murmur at operation. In all cases we have used a stethoscope directly on the heart to establish the point of maxium intensity which ordinarily lies 3·5 cm. below the actual ductus on the conus. Normally when the ductus is compressed the murmur and palpable thrill disappear, but there have been a number of cases in which sounds still persisted. A coarse systolic bruit that disappears in several weeks is fairly common, but there were 4 cases in which the thrill and murmur altered in character and position but still persisted. If we had only recognized this after operation, the possibility of recanalization or failure to close the ductus would have been considered. In these unusual cases complete closure of the ductus was confirmed and additional dissection to exclude other channels was carried out. One of these patients constituted our only fatality: the diagnosis before operation was recorded as a persistent ductus plus a patent auricular septum. The residual murmur, which was that of the patent septum, was heard, and the septum was demonstrated at autopsy. The cause of death was an unrecognized low degree of hæmophilia which led to continued pleural hæmorrhage in spite of the use of anticoagulants and massive blood transfusions. I have emphasized this, because I feel that additional lesions can easily be overlooked, and that our knowledge of the causation of both thrill and murmur is incomplete. On occasions an accidental pressure or kinking of the pulmonary artery has produced unusual sounds, and even mediastinal displacement can add to the confusion. There is also the effects of air or traces of blood in the pericardium to be considered if this sac is nicked during operation.

One cannot exclude the possibility of recanalization if simple ligature is used. I have employed no other method in the series, and am left with two cases which would in many ways serve as examples; both were originally infective cases in which the murmur persisted in an altered character; both are clinically in excellent condition, and in one the diastolic pressure is at normal level; the other maintained a low diastolic all through, even directly after the ductus was tied.

The question of blood pressure has been fully studied, and in children under 14 years the average figure was 106/44 mm. before operation and 104/71 some time after. In adults an average reading of 123/56 went to 128/81, giving a rise in the diastolic level of 25 mm. At the moment of ligature the pressures sometimes rise appreciably and a typical reading was 100/40 before operation, 130/110 immediately after ligature, persisting for 10 to 14 days to stabilize at 96/70. This rise in blood pressure occasionally coincides with a very rapid post-operative pulse rate lasting for a week to a fortnight and not due to any difficulty in lung expansion.

The final point I would make is concerned with the radiographic appearances. On screening the dilated conus and the free active pulsation in the lung root may be recognized, and we have found considerable value in kymography, where we have noted an erratic notching over the conus in a proportion of cases. I am not certain, but feel that this is almost diagnostic, and it has been of help in doubtful cases.

Of other abnormalities that have been encountered at operation, there has been a stricture of the left pulmonary artery, and a large vein resembling a left superior vena cava in size and position which in part entered lung substance.

These points I have brought forward to suggest that diagnosis is not always simple, and that there are an appreciable number of additional complications that may be encountered. Surgery, apart from its therapeutic value, has afforded some light on the pathology of the living, and has certainly led to some doubt as to the reliability of interpretation of classical physical signs.

By O. S. Tubbs, London

I wish to congratulate Dr. Taussig, Dr. Blalock, and Dr. Crafoord on their remarkable work. My experience is limited to 33 patients operated upon with the diagnosis of patent ductus, and my comments are based on this series.

In 32 of these 33 cases, the diagnosis of patency of the ductus proved correct at operation. An additional lesion was almost certainly present in two; in the rest, the ductus appeared to be the only abnormality. A Gibson murmur was present in all the cases except in one child of 8 in whom the murmur was confined to systole; the lumen of the ductus in this latter case proved extremely small.

With regard to the X-ray findings, prominence of the pulmonary artery below the aortic knuckle should not be expected in every case, as it was sometimes completely absent. The sex incidence in the series showed the expected preponderance of females (22 females and 10 males).

Indications and optimum time for operation. Starting in 1939 with an infected case, my experience was for a long time confined to those with infection,

but it is now thought that *all* cases in which a patent ductus is diagnosed as the sole lesion, should be treated surgically at about the age of 7, unless there are special indications to operate earlier. Subsequent to the age of 7, secondary changes and complications, including infection are liable to occur in the untreated case, so that operation should not be delayed much beyond this age.

With regard to an upper age limit, the operation does not become more hazardous after the age of 20. There had been 12 patients over the age of 20 with 2 deaths, and 20 patients under 20 with 3 deaths, *all* the deaths being in infected cases.

The higher mortality in the presence of infection, i.e. 5 deaths in 12 cases (40 per cent) had been the general experience before penicillin became available. This raises the question as to the place of operation in the infected case at the present time. The dramatic reduction in fever and rapid removal of bacteria from the blood stream in such patients is well recognized, but although many patients progress to complete recovery, the mortality is considerable. On these grounds a full course of penicillin should be given, and this should be followed by operation to prevent recurrence. In the penicillin-resistent case the ductus should be closed as soon as the diagnosis had been made. Evidence of systemic embolism in addition to pulmonary infarction is not a contraindication to operation as, although the chance of cure is much less when systemic embolism has become apparent, recovery does sometimes follow.

Cyclopropane had been used as the anæsthetic agent in earlier cases, but ether was now preferred, with curare to diminish the respiratory excursion, as this was less likely to produce cardiac irregularities. With regard to the operation, the posterior approach through the fourth intercostal space was much preferred to the anterior incision, as the cosmetic result was better, and, far more important, it gave a wider exposure so that it would be possible to deal with any accident that might occur.

The best method of closing the ductus remained a subject for discussion as the incidence of recanalization following the various techniques was still argued. The criterion on which recanalization could be diagnosed was also not fully agreed although most workers considered a diastolic murmur as indicative of a leak. The short ductus of large calibre was the type most likely to recanalize following simple ligature, and on these grounds it was probably preferable to divide such cases and suture the two ends.

The changes consequent to closure of the ductus were mentioned, including the immediate rise of diastolic blood pressure, the abolition of the thrill in the pulmonary artery and of the diastolic murmur, and the rapid reduction in the size of the heart, and in the prominence of the pulmonary artery and its branches in the lung field.

Complications were rare. Tachycardia was commonly seen in the first week or ten days after operation, but proved of little consequence. Massive collapse of the left lung or left lower lobe had been seen, but this had not caused serious disturbance. Fluid collection in the pleural sac was occasionally sufficient to require aspiration.

Coarctation of the Aorta

By Crighton Bramwell, Manchester

Sufficient time has not yet elapsed since the introduction of this operation to enable one to tell how much it would add to the span of life, but there is good reason to be optimistic.

In his own series of 36 cases of coarctation, 13 were over 30 years of age at the time they first came under observation. His 3 oldest patients were dead, but all lived to over fifty, and 2 died of conditions unassociated with their coarctation, one of carcinoma of the stomach and the other of lobar pneumonia. Of the other 10 patients over thirty, 9 were still living and many of these were capable of undertaking strenuous physical exertion without any apparent disability. The third decade seemed to be the most dangerous, for many patients were free from symptoms and, being men of good muscular development, were liable to be subjected to severe physical strain; while in the case of women, their first confinement might prove fatal. There seemed to be a fair chance that those who survived the hazards of the third decade might live another twenty years. Should these older patients be operated on, or should we consider that having come safely through the dangerous period from twenty to thirty implied that their coarctation was sufficiently well compensated to make their further outlook more favourable? Perhaps my patients may have been particularly fortunate, since in Maud Abbott's series there were 23 per cent of deaths in the fourth decade.

The sex incidence is difficult to explain. Women with coarctation are less likely to break down because apart from confinement, they are not subject to the same physical strain as men, and

hence they may never be medically examined. This, however, cannot be the whole explanation for even in Maud Abbott's series, which was based on post-mortem statistics, the number of males was twice as great as the number of females. Necropsies, however, were more frequently performed on males.

Regarding cardiac enlargement my experience differs from Dr. Crafoord's. In only 4 of my 36 cases was the heart much enlarged, and in all four there was some additional lesion that would account for the enlargement: three had aortic incompetence and one a freely patent ductus.

MAURICE CAMPBELL spoke of the gradual rise of blood pressure observed directly in some cases and deduced from analysis of all reported cases (*Brit. Heart J.*, 1947, **9**, 203).

S. SUZMAN described a method by which the collateral circulation in the back could be demonstrated or increased (*Brit. Heart J.*, 1947, **9**, 187).

PULMONARY HEART DISEASE ACUTE AND CHRONIC

September 10, 1947, morning. Joint Meeting with Section of Diseases of the Chest

By J. McMichael, London

Heart failure from primary disorder of the lungs may be classified as follows.

Acute. Pulmonary embolism.
Subacute. Miliary carcinoma.
Chronic. (1) Primary pulmonary hypertension.
(2) Secondary to lung disease.
Emphysema (Bronchitis, Bronchiectasis, Cystic disease).
Pneumoconiosis (Silicosis, Anthraco-silicosis).
Pulmonary fibrosis (Fibroid tuberculosis, Scleroderma).
(3) Kyphoscoliosis.

Acute pulmonary embolism. Recognized by circulatory collapse, raised venous pressure, electrocardiographic and other signs of right heart strain.

Chronic cor pulmonale. Commonest cause is emphysema. Capacity of lung vessels in health is approximately 800 ml. and this volume is mainly in the capillaries. Obliteration of half the vascular bed in the lungs by ligation of left pulmonary artery produces no rise of pulmonary artery pressure. Best measurement of anatomical lung damage is percentage of residual air in total lung volume. Normal average 28, range 16–40 per cent; anything over 60 denotes severe emphysema. Optical records of systolic right ventricular pressure also measure pulmonary artery systolic pressure. Normal range 18–30 mm. Hg. In emphysema without heart failure this pressure is often raised, but there is no correlation between residual air percentage and degree of pulmonary hypertension. It is therefore unlikely that anatomical damage to lungs is itself directly responsible for pulmonary hypertension.

In heart failure from emphysema cardiac output is normal or above normal except when blood pressure falls terminally.

High output failure. This group includes (1) subjects with circulatory shunts which are parasitic on normal circulation (arteriovenous aneurysms, Paget's disease of bone), (2) conditions demanding an excessively rapid circulation due to deficiency of available oxygen (anæmia, cor pulmonale), (3) beri-beri. The rapid circulation is achieved by a rise in venous pressure, even though œdema also appears.

Clinical Features. General dusky cyanosis, warm hands, and good peripheral pulse. (Contrast cold blue hands and ears of low output failure resulting from hypertension, valvular and ischæmic heart disease.) Often an exacerbation of chronic bronchitis; in absence of this, orthopnœa strikingly absent. Auricular fibrillation unusual. Terminally pulmonary œdema often present. Radiologically enlargement of pulmonary artery. Electrocardiographic signs of right heart stress.

Treatment. Oxygen tent and penicillin aerosol inhalation. Venesection lowers cardiac output. Digoxin usually does the same, and both procedures may be harmful.

Some clinical varieties. (1) Acute circulatory collapse from valvular pneumothorax or large bulla, due to loss of negative intrathoracic pressure and defective filling of the heart with resulting fall in output. (2) Miliary carcinomatosis. Oxygen saturation of arterial blood falls, cardiac output rises, often with rise in venous pressure. (3) Primary pulmonary hypertension occurs with no disease in lungs other than increased vascular resistance. (4) Scleroderma may be associated with fibroid changes in the lungs and right heart strain. (5) Kyphoscoliosis. Cor pulmonale a well recognized terminal event in such patients.

Lung vessels are sensitive to falling oxygen tension which causes vaso-constriction of pulmonary arterioles (Cournand, Von Euler and Liljestrand). Defective ventilation causes closure of the pulmonary circulation in atelectatic and pneumonic lobes. This reaction may also produce pulmonary hypertension in emphysematous, fibrotic, and miliary carcinomatous lungs.

La Pression Ventriculaire Droite Moyenne (P.V.D.M.) Dans Certaines Affections Broncho-pulmonaires Chroniques

Par J. Lenègre et P. Maurice, Paris

L'hypertension dans la circulation artérielle pulmonaire est considérée depuis longtemps comme un des principaux facteurs qui expliquent l'évolution possible de certaines affections broncho-pulmonaires chroniques vers l'insuffisance ventriculaire droite. Mais cette conception, quoique basée sur des arguments cliniques, radiologiques, électriques et anatomiques, é-tait seulement jusque dans ces dernières années une hypothèse plausible, puisque les médecins étaient incapables de mesurer chez l'homme la pression dans la petite circulation.

Depuis six ou sept ans, des recherches poursuivies aux Etats-Unis, en France et en Angleterre, ont permis de mesurer chez l'homme la pression qui règne dans les cavités droites du cœur et même dans l'artère pulmonaire.

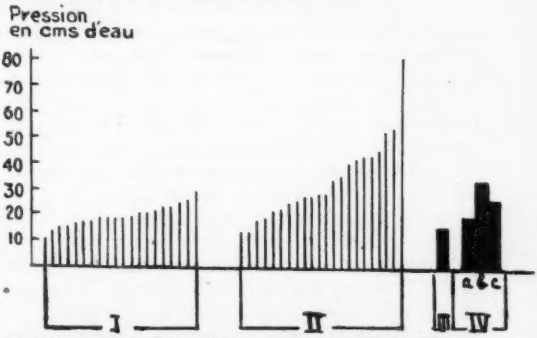
En 1941, Richards *et al*, de New-York, les premiers à notre connaissance, puis en 1944, McMichael et Scharpey-Schafer, de Londres, font connaitre les chiffres de la pression auriculaire droite chez l'homme normal et en état d'insuffisance cardiaque. En décembre 1943, Lauson, Bloomfield, Breed, et Cournand rapportent quelques chiffres de pression ventriculaire droite (systolique, diastolique et différentielle) à l'état normal et chez les cardiaques. En Mai 1944, Lenegre et Maurice exposent leurs premiers résultats de la mesure de la P.V.D.M. chez 51 sujets dotés d'un coeur normal ou atteints de cardiopathies diverses. Depuis, ces recherches se sont multipliées aux Etats-Unis (Bing, Vandam, et Gray, Jr.), au Mexique, au Danemark (Tybjaerg, Hansen, et Warburg), en Suède.

Il est donc inopportun de reprendre en détail la technique actuellement bien connue de la cathétérisation du coeur droit : une sonde stérilisée est introduite asepticquement par une veine du pli du coude (de préférence la basilique) jusque dans l'oreillette droite ou le ventricule droit. Personnellement nous utilisons une sonde uretérale n° 13, longue de 120 centimètres, que nous faisons pénétrer dans la veine par dénudation sanglante ou grâce à un trocart dont le calibre intérieur est de 2,4 mm. Faute d'un matériel plus précis, nous mesurons avec un manomètre anéroïde (Claude) la pression moyenne qui régne dans les cavités droites, notamment dans le ventricule droit. La technique est à la fois sûre et simple. Si elle connait quelques échecs, dûs souvent à des spasmes veineux, elle est inoffensive. Elle n'est suivie d'aucun incident, sauf parfois d'une induration un peu douloureuse et très passagère de la veine ponctionnée.

Nos premières recherches nous ont conduits à considérer que la P.V.D.M. varie suivant les sujets à l'état normal entre 10 et 20 cm. d'eau, soit 7·5 à 15 mm. de mercure. Le chiffre moyen est de 15·5 cm. d'eau, soit 12 mm. de mercure.

Le but de cette communication est d'exposer les chiffres de P.V.D.M. recueillis par 42 explorations chez 41 sujets atteints: 1°—d'une affection broncho-pulmonaire chronique avec ou sans catarrhe bronchique: asthme (8 cas), emphysème (13 cas), silicose ou asbestose (13 cas), tuberculose fibreuse (1 cas), dyspnée de cause inconnue (1 cas); 2°—d'une cyphoscoliose accentuée avec gibbosité (4 cas); 3°—d'une thrombose primitive des deux artères pulmonaires (1 cas). Chez ces 41 malades, l'insuffisance cardiaque, et notamment une insuffisance ventriculaire droite typique (coeur pulmonaire chronique), était présente 10 fois.

Nous avons divisé ces 41 sujets en 2 groupes suivant que leur affection était bien ou mal tolérée. Nous avons admis que les signes suivants étaient les indices d'une mauvaise tolérance : 1°—dyspnée accentuée au repos ou au moindre effort, limitant plus ou moins l'activité sociale; 2°—cyanose; 3°—bruit de galop droit, gros coeur, gros foie, oedèmes des membres inférieurs. Nos résultats sont consignés dans les deux tableaux suivants.



Pression ventriculaire droite moyenne (P.V.D.M.) chez 41 sujets atteints d'une affection broncho-pulmonaire chronique avec ou sans catarrhe bronchique (asthme, emphysème, silicose, sclérose tuberculeuse), ou d'une cyphoscoliose accentuée ou d'une insuffisance ventriculaire droite.
I—Affection broncho-pulmonaire bien tolérée (20 cas). II—Affection broncho-pulmonaire mal tolérée (22 mesures chez 21 malades). III—P.V.D.M. chez le sujet normal (15 cm. d'eau). IV—P.V.D.M. dans les affections broncho-pulmonaires chroniques: a) bien tolérées: 18·7 cm. d'eau: b) mal tolérées: 33 cm. d'eau: c) moyenne générale: 26·2 cm. d'eau.

Il ressort les faits suivants :

(1)—Dans 20 cas d'affection broncho-pulmonaire chronique (ou autre) bien tolérée, la P.V.D.M. est:

—14 fois mormale (10 à 10 cm. d'eau, soit 7·5 à 15 mm. de mercure).

—3 fois à peine supérieure à la normale (21 à 22 cm. d'eau, soit 16 mm. de mercure).

—3 fois modérément augmentée (24 à 28 cm. d'eau, soit 18 à 21 mm. de mercure).

Le chiffre moyen, calculé sur ces 20 cas, est de 18·7 cm. d'eau (14 mm. de mercure), e'est-à-dire voisin de la normale.

(2)—Sur les 22 mesures effectuées chez 21 sujets atteints d'une affection broncho-pulmonaire chronique (ou autre) mal tolérée, la P.V.D.M. est:

—4 fois normale (13 à 18 cm. d'eau, soit 10 à 15 mm. de mercure).

—2 fois à peine supérieure à la normale (21 à 22 cm. d'eau, soit 16 mm. de mercure).

—16 fois franchement ou considérablement augmentée (25 à 80 cm. d'eau, soit 19 à 60 mm. de mercure).

Le chiffre moyen calculé sur les 22 mesures est de 33 cm. d'eau (25 mm. de mercure), soit plus du double du chiffre normal.

(3)—La moyenne générale des chiffres de P.V.D.M., calculée d'après nos 42 explorations chez 41 sujets atteints d'affections broncho-pulmonaires chroniques diverses, bien ou mal tolérées, s'établit à 26·2 cm. d'eau (20 mm. de mercure). Elle est donc franchement élevée.

La confrontation des chiffres de la P.V.D.M. avec les signes cliniques, radiologiques ou électriques, montre que, dans l'ensemble, plus la maladie broncho-pulmonaire est sévère et plus l'hypertension ventriculaire droite est élevée. Le fait est particulièrement évident dans les cas d'insuffisance ventriculaire droite avérée, qui correspondent comme on peut le voir sur le deuxième tableau, aux chiffres les plus forts, à savoir, 35, 40, 41, 42, 44, 52, 53 et 80 cm. d'eau, soit 26 à 60 mm. de mercure.

Dans 6 cas cependant ou la maladie broncho-pulmonaire chronique peut passer pour bien tolérée, la P.V.D.M. est déjà élevéè (21 à 28 cm. d'eau, soit 16 à 21 mm. de mercure). Cette hypertension dans la circulation artérielle pulmonaire représente fort probablement un indice défavorable. L'avenir montrera si l'évolution s'est faite plus rapidement chez ces malades vers l'insuffisance ventriculaire droite.

Inversement, dans 4 cas où l'affection broncho-pulmonaire chronique parait déjà mal tolérée (dyspnée accentuée et parfois cyanose), sans être cependant accompagnée d'insuffisance ventriculaire droite, la P.V.D.M. reste normale (13 à 18 cm. d'eau, soit 10 à 15 mm. de mercure). Ces résultats, un peu insolites, ne s'expliquent pas par des considérations d'âge et de sexe, et leur mécanisme nous échappe encore. Ils sont d'ailleurs relativement rares et n'empêchent pas d'admettre que l'augmentation de la P.V.D.M. marche de pair avec la gravité de la maladie: elle représente probablement un des facteurs décisifs dans l'évolution et le pronostic d'une affection broncho-pulmonaire chronique. Nos recherches semblent donc confirmer l'opinion classique.

Nos constatations sont en harmonie avec celles de Cournand, effectuées à l'aide d'une technique plus précise (enregistrement, avec un manomètre à membrane de Hamilton, de courbes étalonnées de la pression ventriculaire droite, systolique, diastolique et différentielle). Par cette méthode, Cournand admet que chez l'homme normal la pression ventriculaire droite systolique varie entre 18 et 30 mm. de mercure, avec une valeur moyenne de 25 mm. de mercure. Chez 17 sujets atteints d'emphysème ou de sclérose pulmonaire sans gros coeur, la pression ventriculaire droite systolique s'est montrée 4 fois normale (autour de 24 mm. de mercure) et 13 fois élevée (44 à 45 mm. de mercure).

Dans un autre travail, Bloomfield, *et al.* (1946) relèvent les résultats suivants qui portent sur 20 mesures effectuées chez 19 sujets atteints d'emphysème ou de sclérose pulmonaire sans insuffisance ventriculaire droite: pression systolique, 16 à 57·5 mm. de mercure; pression différentielle (pulse pressure), 16 à 54 mm. de mercure. Chez deux autres malades où l'affection se compliquait d'insuffisance ventriculaire droite évidente, la pression systolique était de 35 et 77 mm. de mercure et la pression différentielle de 21 et 68 mm. de mercure. De ses recherches, Cournand conclut:

"(a) That pulmonary hypertension had not developed in cases with moderate degree of emphysema, (b) but that in the group with the most marked degree of emphysema, hypertension in the lesser circulation was present, and finally, (c) that in the group with fibrosis and moderate emphysema and apparently small heart, pulmonary hypertension was already quite marked. For a time, it was our impression that polycythemia played a decisive role in the early development of pulmonary hypertension by increasing the resistance to flow."

Nous avons aussi cherché s'il n'existerait pas des signes cliniques, radiologiques ou électriques susceptibles de faire prévoir l'hypertension dans la circulation artérielle pulmonaire. Le plus souvent, il n'est pas possible d'en inférer du syndrome clinique à la pression ventriculaire droite. Cependant, sur 7 cas où la cyanose était présente, la P.V.D.M. s'est montrée franchement augmentée 5 fois. Sur 4 cas où l'axe électrique du coeur était vertical, la P.V.D.M.

était nettement augmentée 3 fois. Enfin, elle était franchement élevée dans les 4 cas d'axe électrique droit. Ce dernier signe, d'après notre expérience personnelle, parait donc être un indice à peu près certain de forte hypertension pulmonaire. Mais nous ne croyons pas devoir attribuer d'importance à l'amplitude augmentée des ondes auriculaires P dans les deuxième et troisième dérivations, et notre élève Ferrero publiera prochainement ses constatations à ce sujet.

Comme nous l'avons déjà signalé, la présence d'une insuffisance ventriculaire droite d'origine pulmonaire est, elle aussi, un test généralement décisif d'hypertension dans la circulation pulmonaire.

SUMMARY

La pression ventriculaire droite moyenne (P.V.D.M.) est étudiée dans 41 cas d'affections broncho-pulmonaires chroniques (asthme, emphysème, cyphoscoliose, etc. . . .) avec ou sans insuffisance ventriculaire droite.

Chez 20 malades dont l'affection est bien tolérée, la P.V.D.M. est 14 fois normale, 3 fois à peine supérieure à la normale, 3 fois modérément augmentée. Le chiffre moyen, calculé sur ces 20 cas, est de 18·7 cm. d'eau, ou 14 mm. de mercure, c'est-à-dire voisin de la normale (15·5 cm. d'eau ou 12 mm. de mercure).

Chez 21 malades, qui ont permis 22 explorations et dont l'affection est mal tolérée, la P.V.D.M. s'est montrée 4 fois normale, 2 fois à peine supérieure à la normale et 16 fois franchement ou considérablement augmentée (jusqu'à 3 et même 5 fois la valeur normale). Le chiffre moyen calculé sur ces 22 mesures est de 33 cm. d'eau (25 mm. de mercure), soit plus du double du chiffre normal.

Sauf rares exceptions, plus la maladie broncho-pulmonaire est sévère, et plus l'hypertension ventriculaire droite est accentuée. Le fait est particulièrement évident quand existe une insuffisance ventriculaire droite avérée, ou quand l'axe électrique du coeur est dévié à droite.

Dans les affections broncho-pulmonaires chroniques, l'élévation de la pression ventriculaire droite (ou artérielle pulmonaire) représente probablement un des facteurs essentiels de l'évolution vers l'insuffisance ventriculaire droite.

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PULMONARY HEART DISEASE

BY W. D. W. BROOKS, London

I propose in this discussion to examine some of the causes and the consequences of hypertension in the pulmonary circulation, particularly in so far as the lungs are concerned. Hypertension in the pulmonary circulation increases the work of the right ventricle and in certain circumstances may cause pulmonary heart disease. The process may be acute, or may occur gradually and be chronic.

Acute Cor Pulmonale. The most frequent cause is the sudden obstruction of a considerable proportion of the pulmonary circulation by embolism from a systemic venous thrombus usually in the pelvis, abdomen, or leg. The phenomenon not unfrequently follows an operation. Occasionally the embolus derives from the right side of the heart itself. Fat embolism too may give this result. Very rarely an aortic aneurysm ruptures into the pulmonary artery and causes acute cor pulmonale.

No primary pulmonary disorder is known that gives rise to acute cor pulmonale. It has not been reported to occur for example, as a result of blast, irradiation burns of the lungs, or of any acute infection. Spontaneous pneumothorax, even when bilateral, does not have this consequence, presumably because the blood flow into the thorax and through

the lungs is reduced proportionately as the intrapleural pressures increase and the lungs shrink. A respiratory death is the rule.

On one occasion during the war a traumatic diaphragmatic hernia was seen to give rise to acute cor pulmonale. A sailor, aged 27, in 1942 fell down a ladder on a destroyer and was admitted to R.N.H. Chatham eight hours later. Pain in the front of the chest, dyspnœa, and shock were marked features of the case, and he had a very large (left) traumatic diaphragmatic hernia containing the stomach and some coils of intestine, and the mediastinum was grossly displaced. The size of the hernia continued rapidly to increase because the stomach was so kinked on its pyloric attachments that complete obstruction at that level resulted. Increasing systemic venous pressure, enlargement of the liver, together with clinical and radiological evidence of dilatation of the right ventricle became evident. At this time an electrocardiogram showed negative T waves in leads II and III, and a prominent Q in lead III. The passage of a stomach tube and other measures gave some relief, but he died on the operating table. Only one other instance of this sequence of events has been recorded (McGinn, S., and Spear, L. M.: *New England J. Med.* (1941), **224**, 1014).

While considerable attention has been paid to the cardiovascular phenomena in acute cor pulmonale the consecutive pulmonary sequelæ have been somewhat neglected. They are not unimportant. As a direct consequence of the rapid rise in pulmonary vascular pressure the lungs become less easily altered in volume and shape. Respiration thus requires more muscular effort, the intrapleural pressure fluctuates at a more nearly atmospheric level, and may exceed atmospheric pressure during expiration. The chest can be seen to be relatively distended in expiration, so that in the more usual type of case it seems highly probable that despite extensive infarcts the residual air is relatively and perhaps absolutely increased. The vital capacity is reduced, sometimes almost to the level of the tidal air. No doubt pain too contributes to cause shallow respiration. Moreover, there may well be enough distension of the residual patent pulmonary capillaries to reduce the efficiency of gas interchange at the alveolar surface. All this occurs acutely and there is little time for adjustment and compensation to take place, in contrast to what happens when, for example, congestive heart failure supervenes on mitral stenosis. As a consequence, and apart altogether from the cardiac effects respiratory inefficiency acute and severe in degree gives rise to anoxæmia, makes the issue more hazardous, and the need for oxygen therapy more urgent. The later results of pulmonary infarction in those patients who survive are well known and need not detain us.

Chronic Cor Pulmonale. Though the pressure in the right ventricle and pulmonary artery can now be measured directly the procedure is scarcely yet one which can be called a routine clinical method. As a rule, therefore, the diagnosis of pulmonary hypertension depends upon an understanding of the disorders capable of producing it, and upon the recognition of the clinical features that they may produce.

These disorders are numerous but they fall into four groups:

(1) obstruction of the pulmonary circulation within its own limits, e.g. in emphysema, and in certain pulmonary fibroses;
(2) obstruction of the pulmonary circulation beyond its structural limits, e.g. in the left ventricular failure, and in mitral stenosis;
(3) shunting of blood from the arterial into the pulmonary circulation in, e.g. certain instances of congenital heart disease; and
(4) in severe deformity of the thoracic bony structures, e.g. severe kyphoscoliosis.

In conformity with our original limitation discussion will be restricted to the association of emphysema and pulmonary fibrosis with pulmonary hypertension and chronic cor pulmonale.

Symptoms and Signs. Dyspnœa is the outstanding symptom. It is, of course, a major clinical feature of both these disorders but with the advent of pulmonary hypertension it becomes progressively worse and ultimately incapacitates the patient. Cough is frequently but not always present, and it is productive when chronic bronchitis or passive congestion of the lungs complicate the case. When the right ventricle fails the systemic veins become more distended, the liver enlarges and often becomes tender, and œdema, ascites, oliguria, and sometimes nausea and vomiting occur.

When the heart enlarges it is the conus arteriosus and right ventricle that are predominantly concerned, and the latter, occupying a greater proportion of the heart's anterior surface than is normal may give rise to visible and palpable pulsation in the third and fourth left intercostal spaces. The pulmonary second sound is accentuated, and later gallop rhythm may be heard. Less constant and very variable features are cyanosis, clubbing of the fingers and toes, and polycythæmia. To these will be added the well-known symptoms and physical signs of the underlying pulmonary abnormality. It will be observed that a majority of the clinical features of pulmonary hypertension are also features of emphysema and of certain pulmonary fibroses such as the pneumokonioses. Only when failure

of the right heart develops, do distinctive symptoms and signs arise. For this reason, the early recognition of pulmonary hypertension is greatly helped by radiological examination. The distended pulmonary vessels can as a rule be seen spreading far out into the lungs, and the aggregate of major pulmonary vascular trunks at the hila are much more dominant a feature than is usual. I am indebted to my colleague, Dr. E. Rohan Williams, for his demonstration that enlargement of the pulmonary artery near the hilum can often especially well be shown by radiography in the lordotic position. Tomography also can demonstrate these dilated vessels beautifully.

It has long been assumed that emphysema causes pulmonary hypertension and ultimately cor pulmonale by progressive obliteration of the capillaries within the lungs. The major weakness in this hypothesis is the lack of correlation between the degree of emphysema and the accompanying cardiovascular change. Parkinson and Hoyle (1937) (*Quart. J. Med.*, **6**, 59) summarize the historical background and set forth this difficulty so well that I need only cite this one report. In the last ten years the part played by consecutive arteriosclerotic changes particularly in the pulmonary arterioles has been emphasized in several reports of which (Parker, R. L. (1940), *Ann. intern. Med.*, **14**, 795; and Gilmour, J. R., and Evans, H. (1946) *J. Path. Bact.*, **56**, 587) are noteworthy. The last authors in a case of primary pulmonary hypertension reported aplasia or hypoplasia in innumerable small pulmonary arteries, and concluded that this deficiency was a factor leading to the later genesis of endarteritis and pulmonary hypertension. From these reports it would seem likely that in emphysema associated arteriosclerosis in the pulmonary arterioles is a requisite for the development of cor pulmonale. It is not yet clear to what extent in emphysema the obliteration of capillaries and hypertension from this source causes arteriolar sclerosis. Cases occur in which pulmonary arteriosclerosis arises independently of any pulmonary disease or indeed of any known cause so that other factors may be concerned. There are few if any comparable investigations in patients with pneumonokoniosis.

It was thought worth while to investigate series of normals, of emphysema, and of pneumonokoniosis with and without pulmonary hypertension, and to compare the cardiac output, cardiac area, and lung volumes in these series in the hope that some correlation between the pulmonary pathology and the extent of the pulmonary hypertension might be found.

Results

The results of the estimation of the cardiac output and lung volumes in 12 normal controls of similar ages to those of the cases of emphysema and fibrosis are set forth in Table I. Basal conditions obtained throughout.

Cardiac output showed a variation dependent on difference in size of the individuals, the cardiac index being nearly constant. Mean C.I. = 2·2 lit. per sq. metre: probable error $\pm$0·083. The cardiac area as determined by a planimeter from standard postero-anterior radiograms was 173·3$\pm$5·11 sq. cm. The value of the total pulmonary capacity and its subdivisions, the vital capacity and residual air, fell within the limits of normality in regard to both relative and absolute values of these quantities.

Emphysema. Fifteen male patients were investigated. Their physical and clinical characteristics, the duration of symptoms, the signs, and the X-ray and cardiographic findings were recorded. Their disability ranged from dyspnœa on moderate exertion to dyspnœa at rest. Cyanosis, while the

TABLE I

NORMALS

Case	Cardiac output	Cardiac index	Cardiac area	T.P.C. *	V.C. *	R.A. *	$\frac{RA}{TPC}\times 100$
1	3·70	1·74	204	7·08	5·80	1·28	18·1
2	4·26	2·23	168	6·57	5·30	1·27	19·3
3	4·38	2·11	202	5·27	4·19	1·08	20·5
4	2·47	1·44	191	6·56	4·90	1·66	25·3
5	3·56	1·99	189	5·46	3·95	1·51	27·7
6	5·04	2·93	128	4·66	3·48	1·18	25·3
7	4·46	2·13	152	7·80	5·70	2·10	26·9
8	4·06	2·06	181	7·10	5·10	2·00	28·2
9	3·92	2·20	133	4·47	3·20	1·27	28·4
10	3·14	2·11	145	3·76	2·64	1·12	29·8
11	5·38	3·18	193	4·31	2·95	1·36	31·5
12	4·71	2·35	187	8·56	5·73	2·83	33·1

* T.P.C., total pulmonary capacity; V.C., vital capacity; and R.A., residual air.

TABLE II

EMPHYSEMA

Case	Cardiac output	Cardiac index	Cardiac area	T.P.C.	V.C.	R.A.	$\frac{RA}{TPC}\times 100$
13	6·96	3·36	213	5·73	4·04	1·69	29·5
14	7·60	4·04	184	6·45	4·54	1·91	29·6
15	4·51	3·30	194	4·11	2·72	1·39	33·8
16	8·30	4·19	268	7·71	4·95	2·76	35·8
17	3·59	2·05	192	5·55	3·50	2·05	36·9
18	6·36	3·60	174	4·54	2·74	1·80	39·7
19	7·39	3·47	206	4·29	2·56	1·73	40·3
20	4·34	2·89	169	6·58	3·92	2·66	40·4
21	6·13	4·41	129	4·20	2·48	1·72	41·0
22	4·72	2·36	210	6·47	3·80	2·67	41·3
23	3·26	1·71	165	5·46	3·18	2·28	42·2
24	5·84	3·06	181	6·90	3·80	3·10	44·9
25	4·94	3·38	114	4·66	2·46	2·20	47·2
26	3·74	2·63	109	4·77	2·04	2·73	57·2
27	5·30	2·76	299	5·84	1·77	4·07	69·6

patient was resting, was present in eight, but clubbing of the fingers was noticeable in one patient only. In two cases (16, 27) the chronic pulmonary disorder was complicated by hyperpiesis. Pulmonary hypertension could be diagnosed in eleven cases, and cor pulmonale in five—as a result of an aggregate of the above and subsequent findings. (Cases 13, 16, 17, 18, 19, 20, 22, 23, 24, 26, 27: and 13, 16, 19, 22, and 27 respectively).

In Table II the cases (as in Table I) are set forth in order of the severity of the emphysema as measured by the relative size of the residual air $\frac{RA}{TPC}\times 100$. No correlation could be found between this ratio and the estimated degree of pulmonary hypertension, nor with the incidence or severity of cor pulmonale when that was present.

The cardiac output and index were as a rule higher than had been found in normal controls, and this was also true in cases with cor pulmonale.

The cardiac area, apart from Cases 16 and 27, both of which had systemic hypertension, was essentially the same as that found in the normal controls; the mean cardiac area being $172{\cdot}7\pm 6{\cdot}6$ sq. cm. Vital capacity was reduced, residual air increased so that $\frac{RA}{TPC}\times 100$ was increased. The total pulmonary capacity was not greatly abnormal.

Fibrosis. A similar investigation of 14 cases of pneumonokoniosis was undertaken. Dyspnœa was an even more noticeable feature and cyanosis at rest was apparent in 9 cases.

Six patients had been sand blasters, five coal miners, and one an iron moulder, while in two no recognized industrial hazard productive of pneumonokoniosis had occurred in their history. The duration of exposure was noticeably short in those whose occupation had been sand blasting. In four cases electrocardiography showed left ventricular preponderance and two of these presented evidence of systemic arteriosclerosis and a high blood pressure.

In Table III the degree of pulmonary fibrosis varied from slight to very severe as judged radiologically, but the X-ray findings bore little or no relation to the patient's disability as measured by dyspnœa or to the ratio $\frac{RA}{TPC}\times 100$. In five (Cases 30, 37, 39, 41) pulmonary hypertension could be diagnosed and in two (Cases 30 and 37) cor pulmonale was present. Again there was no correlation to be found between the severity of the respiratory disorder as measured by $\frac{RA}{TPC}\times 100$ and the observed consecutive cardiovascular abnormality or between the latter and the radiological extent of the disease. Cardiac output was often raised and this was true also in those with cor pulmonale. The mean cardiac area (excluding the two cases with systemic hypertension) was $185{\cdot}8\pm 4{\cdot}9$ sq. cm. which showed a slight statistically significant increase as compared with the normals.

The total pulmonary capacity was decreased as a result of a marked decrease in the vital capacity, the residual air being absolutely and relatively increased.

These results confirm previous findings that correlation is lacking between the severity of emphysema and the associated degree of pulmonary hypertension and cor pulmonale. They also show a similar lack of relationship to obtain in cases of pneumonokoniosis—which has not previously been reported.

TABLE III

FIBROSIS

Case	Cardiac output	Cardiac index	Cardiac area	T.P.C.	V.C.	R.A.	$\frac{RA}{TPC} \times 100$
28	4·54	2·40	161	2·88	2·20	0·68	23·6
29	3·81	2·25	237	5·32	3·87	1·45	27·2
30	5·28	3·03	203	4·58	3·16	1·42	31·0
31	7·48	3·84	168	4·36	2·68	1·68	38·5
32	2·92	1·90	155	4·01	2·30	1·71	42·6
33	4·77	3·11	183	3·99	2·24	1·75	43·8
34	2·87	1·95	180	2·75	1·54	1·21	44·0
35	4·89	3·09	168	4·12	2·18	1·94	47·0
36	4·68	2·56	157	4·33	2·22	2·11	48·7
37	4·77	2·69	222	4·35	2·18	2·17	49·9
38	2·98	2·07	176	7·20	3·24	3·96	55·0
39	6·13	3·29	306	3·55	1·50	2·05	57·7
40	8·98	6·36	170	4·48	1·68	2·80	62·5
41	6·25	3·80	282	3·89	1·06	2·83	72·7

In both emphysema and pneumonokoniosis progressive obliteration of small pulmonary vessels occurs which could theoretically ultimately cause pulmonary hypertension. In both disorders the distruction of available effective alveolar surface for oxygenation could give rise to decreased arterial oxygen saturation of the blood and so in turn theoretically cause a "work hypertrophy" and ultimately failure of the heart. In neither disease, however, can the severity of the pathological process be directly related to the observed associated cardiovascular change; and therefore it seems probable that when pulmonary hypertension or cor pulmonale develops some other causal factor, unrelated to the primary pulmonary disease, must be present.

ELECTROCARDIOGRAPHIC APPEARANCES IN ACUTE AND CHRONIC PULMONARY HEART DISEASE

BY PAUL WOOD, London

An analysis of the electrocardiographic appearances in 20 cases of massive pulmonary embolism with raised jugular venous pressure was presented. Limb leads showed an almost constant S wave in lead I, frequent Q wave in lead III, inversion of T III, flattening or slight inversion of T II, and rather low voltage. Occasionally P II was tall and sharp. Multiple chest leads revealed inversion of T from V 1 to V 3 or 4 in all, reversion to normal taking three to six weeks. Transient right bundle-branch block occurred in three. The changes were attributed to acute right ventricular stress.

In 100 cases of chronic pulmonary heart disease, limb leads showed a tall sharp P wave in 85, right axis deviation in 46, a tendency to right axis deviation in 11, a prominent S wave in all leads in 9, right bundle-branch block in 4, and low voltage in 40. Multiple chest leads showed normal ventricular deflections in the majority; inversion of T from V 1 to V 3 occurred in only 13 per cent and a chiefly upright QRS complex in V 1 with a conspicuous S wave in V 5 was seen in only 16 per cent. In another 16 per cent of cases anterior chest leads from V 1 to V 5 revealed a fixed RS pattern with S dominant. It was concluded that the tall spiked P wave was by far the most significant change.

The rest of the communication summarized the author's investigations into this P wave. In normal controls the maximum auricular deflection very rarely measured more than 1·5 mm. in amplitude and averaged 1 mm. The pulmonary P wave commonly ranged between 2–3 mm. in height, but was never widened. It was never seen in normal vertical hearts which refuted the suggestion that it depended on cardiac rotation due to emphysema. It could not be attributed to anoxia for it was an early finding and tended to diminish in voltage when anoxia became severe, nor was it present in cases of severe anæmia. It could not be ascribed to an elevated cardiac output; for it was seen in a much less conspicuous form in cases of thyrotoxicosis in which the cardiac output was considerably higher; moreover, as already mentioned, P was of low voltage in severe chronic anæmia with outputs up to 14 litres a minute. Intracardiac pressure studies failed to reveal any correlation between this P wave and the right auricular pressure, but there appeared to be some association between it and the right ventricular pressure. Just on what such a relationship might depend was unknown.

THE CLINICAL VALUE OF CHEST LEADS

September 10, 1947, afternoon. Section of Cardiology

By Frank N. Wilson,* Ann Arbor, Michigan

In the growth of electrocardiography as a clinical method, British physiologists and physicians have played a more important role than those of any other nationality. Waller was the first to show that the electrical activities of the human heart could be recorded by leading from the extremities or from the surface of the chest. Mackenzie, although he did not deal directly with this subject, tremendously increased our knowledge of clinical disorders of the rate and rhythm of the heart beat and aroused a world-wide interest in this field. Thomas Lewis contributed more than any other man to the development of the principles and methods of analysis upon which the interpretation of the electrocardiogram is founded. Most of my own electrocardiographic studies have been the result of ideas derived from his investigations, and I am also deeply indebted to him for help and encouragement on many occasions. I consider it a very great honour to be asked to discuss an important aspect of clinical electrocardiography here in his native land and in this great city where his work was done. It would have been a still greater pleasure to come here if he were still living and could take part in this discussion.

It was the work of Lewis and Rothschild on the spread of the excitatory process that first aroused my interest in the possibility of exploring the anterior ventricular surface by placing one electrode on the præcordium and the other far from the heart. The observations and ideas contained in their paper and notions derived from a study of the physical principles upon which the work of Einthoven and that of Waller on the electrical axis of the heart is clearly founded led to a series of investigations concerned with the character of the heart's electrical field. These investigations were first undertaken late in 1919 and were continued off and on through the early twenties. A preliminary report to the effect that præcordial leads of the kind mentioned are semi-direct leads very similar to the unipolar direct leads first used by Lewis and Rothschild was published in 1926, but the systematic use of multiple leads of this sort at the University of Michigan dates from the summer of 1929. It was precipitated at that time by the observations on bundle branch block by Barker, Macleod, and Alexander, and was undertaken with the purpose of obtaining additional data bearing on their conclusions. A preliminary report of this work was published in 1930; the final report came out in 1932, and was nearly simultaneous with the paper on the use of a single chest lead in the diagnosis of infarction by Wolferth and Wood. Since that time the percentage of cases in which præcordial leads are employed has steadily increased. We have never taken præcordial leads routinely.

For the purpose of studying disturbances of the rate and rhythm of the heart beat, or of the time relations and sequence of auricular and ventricular activation, unipolar chest leads are only occasionally better than limb leads, and are not in general superior to bipolar chest leads of the kind used by Lewis in his studies of auricular fibrillation, and are much less useful than œsophageal leads. They have not thus far proved to have any special advantages in the study of the form of the auricular complex. On the other hand, chest leads and particularly unipolar leads from the præcordium, are indispensable for the detection and differentiation of abnormalities of the ventricular complex. They frequently disclose abnormalities of the QRS group, the T complex, or both, when the limb leads show either no deviation from the normal or none that have diagnostic significance. On this occasion, it will suffice to consider only those conditions in which the value of unipolar præcordial leads has been most clearly demonstrated. It should, of course, be clearly understood that clinical diagnosis should seldom, if ever, be made on the basis of electrocardiographic findings alone. To rely solely upon an interpretation of the electrocardiogram that is not supported by the case history or other clinical data after an adequate investigation has been made frequently means to run the risk of converting an essentially normal person into a psychoneurotic invalid.

Præcordial leads are of value, first of all, in the recognition of abnormalities affecting the intraventricular conduction of the cardiac impulse. They make it possible in the vast majority of the cases in which the QRS interval measures 0·12 second or more to ascertain whether one is dealing with right bundle branch block, left bundle branch block, arborization block, Wolff-Parkinson-White

* Working under a grant from the Kresge Foundation, University of Michigan.

syndrome, or a conduction defect not belonging in any of these catagories. Intraventricular conduction defects that produce a less striking increase in the QRS interval are somewhat more difficult to differentiate, but præcordial leads often disclose the presence of incomplete right branch block when the ventricular complexes of the limb leads are not distinctly abnormal. They also make it possible in many instances to recognize such combinations as complete or incomplete right branch block plus right ventricular hypertrophy or myocardial infarction, and left bundle branch block plus left ventricular hypertrophy. The electrocardiographic diagnosis of left bundle branch block plus infarction is in our experience rarely possible. Incomplete left branch block is difficult to distinguish from the effects of preponderant hypertrophy of the left ventricle. Many have expressed the opinion that all defects in intraventricular conduction have the same clinical significance and that it is not worth while to attempt to differentiate one from another. The answer to this objection is that we cannot tell whether it is valid until the differentiation in question can be made with reasonable certainty. In the past this has not been possible, and the older studies of the significance of the different varieties of intraventricular block which were based on limb leads can no longer be considered definitive. There are some clinical disorders that produce one type of intraventricular block exclusively or much more often than any of the others. Right bundle branch block is common in pulmonary embolism, Chagas disease, infarction of the ventricular septum, and congenital cardiac anomalies in which the septum is defective; left branch block does not occur at all in some of these conditions and is rare in others. True arborization block is usually, if not always, a consequence of old infarction.

In the second place, præcordial leads are of very great value in the diagnosis of preponderant hypertrophy or enlargement of one ventricle, and particularly in the diagnosis of preponderant hypertrophy or enlargement of the right ventricle. The last is not infrequently induced by pulmonary hypertension, which is often difficult to detect by clinical means. The systematic electrocardiographic study of all cases of heart disease of obscure origin will disclose many cases of unsuspected cor pulmonale. Many patients with congenital heart disease are now candidates for cardiovascular surgery. The use of præcordial leads in such cases frequently yields valuable evidence bearing on the presence or absence of suspected or unsuspected complications. It is now clear that the position of the mean electrical axis of the QRS deflections is determined not by the relative weight or size of the two ventricles, but by the position of the heart in the chest. This is not wholly determined by the nature of the cardiac lesion present. Thus it is possible to have right axis deviation in a case of preponderant enlargement of the left ventricle or left axis deviation associated with preponderant enlargement of the right ventricle.

Finally, chest leads find their greatest field of usefulness in the diagnosis of myocardial infarction, and I have seen a great many instances in which this condition was certainly present and not recognizable by any other method. There are a great many infarcts of the less extensive sort that can be easily recognized if præcordial leads are taken, and nevertheless give rise to no constitutional symptoms whatsoever and to only the most trivial complaints. The infarcts that are least likely to produce characteristic changes in the limb leads but regularly give rise to such changes in præcordial leads are those that involve the anterior part of the ventricular septum and adjacent parts of the anterior wall of the left ventricle. We speak of these as anteroseptal infarcts. Other types of infarcts that produce more striking changes in præcordial leads than in the limb leads are those associated with right bundle branch block, which usually involve the upper ventricular septum, those that for some reason give rise to small bizarre deflections in all of the standard limb leads, and certain posterior or high lateral infarcts. It is desirable to take præcordial leads in all cases in which myocardial infarction is considered a possibility and in all cases in which symptoms of cardiac weakness or cardiac failure develop rapidly without obvious cause. If this is done many instances of clinically undiagnosed examples of infarction will be discovered.

In considering abnormalities of the form of the ventricular complex, particularly those of a nonspecific kind, it is necessary to ask one's self whether they are the result of (1) a minor congenital anomaly, (2) some long past illness which has left behind an anatomic or physiologic scar, (3) an acute process, such as acute myocarditis, myocardial infarction, pericarditis, or toxæmia, or (4) a slowly progressive degenerative condition such as coronary atherosclerosis. Perhaps a fifth possibility, derangement of the vegetative nervous system should be added. In reaching a decision it is often necessary to repeat the electrocardiographic examination at intervals over a considerable period. If the electrocardiographic changes persist unchanged, they should not be ascribed to an acute process. It is also imperative that the final conclusions be based on a careful scrutiny of all the clinical and laboratory data available, and not upon the electrocardiogram alone.

By C. W. Curtis Bain

This communication has been published in fuller form (*Brit. Heart J.*, 1948, **10**, 9).

By Terence East

After hearing Dr. Wilson's address and studying his writings, it is clear that unipolar leads can afford valuable information, more clear than any hitherto available. The difficulty is that the full electrical exploration of the heart may involve the taking of so many records. If one uses the three standard, the six unipolar chest, with perhaps an abdominal or epigastric, the three unipolar limb leads and, possibly, other thoracic and an œsophageal lead, one may end by taking some fifteen or sixteen tracings. For ordinary clinical practice this is too many ; time does not permit such elaboration; one must now begin to consider whether a new approach may not be adopted which will reduce the initial number of leads used: further exploration can be done to elucidate details, but it might be possible to cut down the number taken at first; or perhaps select special leads suitable for obtaining special information. This seems more logical than just using the standard leads and one or more præcordial leads at random. This method must surely become obsolete in the near future.

Definite information can be sought from the cardiogram on the following points. The answer is often final and conclusive.

1. Auricular activity. This is essential in the interpretation of most of the arrhythmias, especially circus movements, and in the study of auriculo-ventricular conduction.
2. Intraventricular conduction and bundle branch block.
3. Indication of unilateral or bilateral ventricular hypertrophy and strain.
4. The position of the heart.
5. Pathological changes in the myocardium; in particular ischæmic disease, and the detection and localization of infarcts; and also unspecific minor variations from the normal.
6. Pulmonary embolism and infarction. This might come under heading 3.
7. Pericarditis, with or without effusion.

To a certain degree the three standard leads have for long revealed a good deal on these points; the addition of chest leads was the first extension into further fields of exploration. The choice of chest contacts is wide; both in site of application; and also whether a unipolar or paired technique should be used. It would appear that there are good reasons for employing the unipolar præcordial technique rather than using a distal electrode on the right arm or left leg. There are also good reasons for using unipolar limb leads, rather than the standard, for thereby true single changes of potential are recorded rather than the differences between two. Apart from the six præcordial contacts, running from right to left, there are others that have been proposed. One of the most promising was the right upper abdominal, which, by a high positive deflection, might be useful as an indication of hypertrophy of the right ventricle. This is not the case, for it has been found that such deflections are given in this lead by vertical hearts, which are actually normal. One might suggest that a practical solution of the difficulties arising from the taking of so many leads is to select the following, for the reasons that are appended.

Lead V 1.

1. This will show auricular waves, and be useful for circus movements, auricular tachycardia, and for measuring auriculo-ventricular block.
2. A large R and small S will show right ventricular hypertrophy.
3. The position of the intrinsic deflection in a prolonged QRS will diagnose the site of bundle branch block.
4. The size of the normally negative deflection will show the position of the heart.

Lead V 4 (*or* V 5). The one selected depends on the size of the heart; it should be just outside the apex beat. (V 6 or 7 might on occasion be needed.)

1. Hypertrophy of the left ventricle is shown by the large R and no S wave. T may be negative (as in standard lead I). Digitalis effects are shown.
2. Anterior infarcts are shown by Q and changes in RS–T junction and T waves.
3. Bundle branch block location is confirmed by the position of the intrinsic deflection in a prolonged QRS.
4. Possibly changes due to pericarditis.

Lead VL. (The unipolar left arm lead.)

1. This may reveal some lateral infarcts.
2. The position of the heart is shown, particularly when vertical, the normally positive leads becoming small or negative.
3. One might expect changes due to pericarditis.

Lead VF. (The unipolar left leg lead.)

1. Posterior infarcts are shown.
2. The changes of pulmonary infarction are detected.

3. The position of the heart is shown, particularly when horizontal.

4. One might expect changes due to pericarditis.

By giving the third strip on the film two separate exposures V L and V F can be shown consecutively, and all four leads will then appear on one film. It is intended to adopt this selective technique on a series of cases, controlled by the standard leads, to determine whether the latter can ultimately be dropped altogether. It may at any time be desirable to amplify the preliminary data obtained by such an approach with full electrical exploration of the heart, using such additional leads as may seem indicated.

By Camille Lian, Paris

After the very interesting communication of Dr. Wilson and Dr. Bain, I shall only say a few words about two chest leads that I have specially studied.

First, the auricular lead which I have named S 5; the right arm electrode is placed on the middle of the sternal manubrium and the left arm electrode on the anterior extremity of the fifth right intercostal space. In this way, the auricular waves are well recorded even when they are invisible in the limb leads. For the same purpose, I have recently employed with success the well known chest leads CF 1 and V 1, but the chest lead S 5 gives better results.

For another purpose, I have used the chest lead BF (back-foot) or VB (back-central terminal of Wilson). After placing the exploring electrode in the standard position, 1, 2, 3, 4, etc., I place it midway between the left scapula and the spine, two fingers above the inferior angle of the scapula. In this lead, the T wave is negative in healthy subjects.

As you know, in cases of coronary disease giving the T III type of curve in limb leads, the T wave generally keeps its normal direction in standard chest leads. But these same cases generally show a reversal of T wave in the chest lead BF or VB, taken as described; that is to say the normally negative T wave becomes positive.

Therefore, in a case presenting an inverted T in lead III, this special chest lead may be informative, for if the inverted T III is due to coronary occlusion, the chest lead BF generally shows a reversal of T, that is a positive instead of a negative T wave. The chest lead BF of VB can thus be useful in cases presenting the T III type of electrocardiogram.

THE USE OF THE PHONOCARDIOGRAPH IN CLINICAL CARDIOLOGY

September 11, 1947. Section of Cardiology

By William Evans, London

The phonocardiograph was born soon after the electrocardiograph, but their growth has been unequal in that the latter has been applied immediately to clinical medicine and has flourished while the former test, used to display such murmurs as the presystolic and the one identified with patent ductus arteriosus, has become largely exhibitional and for that reason has lost ground. More recently, however, phonocardiography has shown signs of coming into its own, and he now predicted for it a place in cardiology not far behind electrocardiography. He proposed to show some of the ways in which the test had already contributed to our knowledge and to point the way in which it could be usefully developed in the future.

In the first place, it had confirmed the clinical classification for *Triple Heart Rhythm*. Such a classification had become necessary owing to the confused terminology connected with this rhythm. All cases of triple heart rhythm fall naturally into three groups. First, from addition of the third heart sound which immediately follows the second sound; secondly, from addition of the fourth heart sound which immediately precedes the first heart sound, and thirdly, from addition of a sound in late systole. This third variety was an innocent condition and only assumed importance in its differentiation from the presence of the third heart sound.

The first kind of triple heart rhythm was found in healthy subjects and in those conditions that produce right heart failure: this included mitral stenosis, hypertensive heart failure, emphysema, pulmonary embolism, primary pulmonary hypertension, auricular septal defect, constrictive pericarditis, cardiac infarction, and anæmia. He spoke briefly about each of these forms of triple heart rhythm.

The second variety from addition of the fourth heart sound was found in prolonged A-V conduction or in left ventricular heart failure as in hypertensive heart failure, aortic incompetence and failure, and in cardiac infarction.

Turning to *Heart Murmurs*, he stressed the importance of the phonocardiograph in confirming the reliability of certain clinical signs which had been assembled for the differentiation of innocent heart murmurs into five main varieties, and he outlined such signs. Concerning the murmurs of organic heart disease he mentioned how common it was for the phonocardiograph to show that the systolic murmur of mitral disease actually occurred during auricular systole as in the case of the presystolic murmur. The mid-diastolic murmur of mitral stenosis was even more important in the light of this newer test, so that in 74 cases of undoubted mitral stenosis the test had shown the presence of this murmur in all of them, but more cases need to be tested before one could say that it was an invariable finding. He then dealt with the murmurs of aortic valvular disease, hypertension, congenital heart disease, anæmia, and heart block.

Dr. Evans believed in the importance of the test not only for research purposes but also for clinical diagnosis in specific instances. The test had come to stay. We would not be able to live without it and for the good reason that our patients would not be able to live so well without it.

In conclusion, he stressed three things in clinical auscultation. First, the advantage to clinical diagnosis of finding and placing the added heart sound which created a triple heart rhythm. Secondly, that the quality and intensity of murmurs matter far less than their place in the cardiac cycle and in relation to the heart sounds. Thirdly, and above all else, the phonocardiograph had emphasized the importance of self catechism during clinical auscultation. He mentioned six questions which should be applied when the bell of the stethoscope rested on any part of the chest in the search for heart disease.

By Camille Lian, Paris

I appreciate the honour of being invited to attend this International Conference and to address the Section of Cardiology. I have been specially interested in phonocardiography for many years and, together with a distinguished qualified engineer, Mr. Minot, have succeeded in designing an original

phonocardiograph, known in France as the Lian-Minot Telestethophone. With this apparatus it is possible to record the heart sounds while actually hearing them reproduced by loud-speaker, a feature of capital importance. The electrocardiogram and the apex impulse can be recorded simultaneously with the heart sounds.

I propose to speak to-day about triple rhythm which I regard as the principal indication for employing phonocardiography in the clinic.

I shall first consider *that variety of triple rhythm in which the second sound is single, and where we have to distinguish between gallop rhythm and a reduplication of the first heart sound* (Fig. 1 and 2). The clinical diagnosis is usually easy—in gallop rhythm, the extra sound is separated from the first heart sound by a silent interval, but there is no silent interval between the two constituents of a reduplicated first sound. However, I have established by phonocardiography that, exceptionally, this silent interval between the gallop sound and the first sound is lacking, and I have described this particular phenomenon as *delayed presystolic gallop* (galop présystolique retardé) (Fig. 3). In this case, the clinician is likely to make the serious error of mistaking a gallop rhythm, which signifies left ventricular failure, for a reduplicated first sound which is a sign of little importance. *Here the phonocardiograph triumphs over the stethoscope.* In the phonocardiogram, if the first constituent of the double sound precedes the summit of the R wave of the electrocardiogram, then we are dealing with a presystolic gallop. If, on the other hand, both constituents of the double sound fall after the summit of the R wave, then we are dealing with a reduplication of the first heart sound.

These remarks apply to records obtained by *the Lian-Minot phonocardiograph which is not sensitive to vibrations of low frequency, for its curve of sensitivity is almost identical with that of the human ear. For this reason, in my phonocardiograms of healthy subjects, no part of the vibrations belonging to the first sound occurs before the summit of the R wave of the electrocardiogram.* Recently, in the United States, Rappaport and Sprague have supported the view that a phonocardiograph should have the same curve of sensitivity as that of the ear. Contrary to the opinion of the Argentine authorities, they consider, as I do, that the vibrations constituting the normal first heart sound never occur earlier than the summit of the R wave of the electrocardiogram. Therefore, both components of a reduplicated first sound are always later than the summit of the R wave. I have also established, both clinically and by phonocardiograph, that there are *arterial reduplications of the first sound,* for aortic or pulmonary vibrations of appreciable magnitude are added to the ventricular vibrations which constitute the first sound. In these arterial reduplications there is a protosystolic snap of maximum intensity at the right or left second or third intercostal space.

I now come to *the second variety of triple rhythm in which the first sound is single. Here the diagnosis lies mainly between a reduplication of the second sound and the triple rhythm of mitral stenosis.* I say this because I have established both clinically and by phonocardiography that *the triple rhythm of mitral stenosis is constituted not by a reduplication of the second sound but by the opening snap of the mitral valve* (Fig. 4).

Triple rhythm in mitral stenosis may also be due to an initial reinforcement of the diastolic murmur, which is characteristic, or sometimes to a reduplication of the second sound which is not characteristic as it occurs in many other conditions. It is therefore important to distinguish a reduplicated second sound, which is not peculiar to mitral stenosis, from the opening snap of the mitral which is quite characteristic (Fig. 5).

I give the following rules for making this distinction. On auscultation, a reduplicated second sound is best heard in the second or third left intercostal space, and the mitral opening snap in the fourth or fifth left space, or less often near the apex. I have also found that a reduplicated second sound is inaudible immediately above the sternum (namely, in the suprasternal notch), while the opening snap is often audible at this site.

In phonocardiography, I prefer to record the apex impulse electrically, as can be done by the electrokymograph of the Lian-Minot apparatus. In such records, the second constituent of a reduplicated second sound occurs during the descent of the apex curve, between points C and D. The mitral opening snap occurs at point D, and the initial reinforcement of the diastolic murmur, still later, at point E.

It is not essential to record the apex impulse in order to identify these three varieties of triple rhythm, for it can also be done by measuring the time interval between the second heart sound and the extra sound. In the case of a reduplicated second sound, the extra sound occurs from 0·03 to 0·07 sec. after the commencement of the second sound. In the opening snap of the mitral, this interval is 0·07 to 0·11 sec., and in the initial reinforcement of the diastolic murmur it is 0·10 to 0·17 sec.

In the diagnosis of mitral triple rhythm, there are several other possible sources of error to be considered. There is the snap I have described as the *late systolic pleuro-pericardial snap* (Fig. 6) which

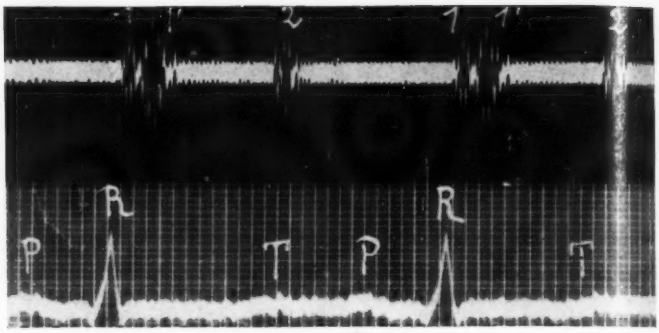

FIG. 1.—*Reduplication of the first sound.* The two groups of vibrations constituting the first sound both occur after the summit of the R wave in the electrocardiogram.

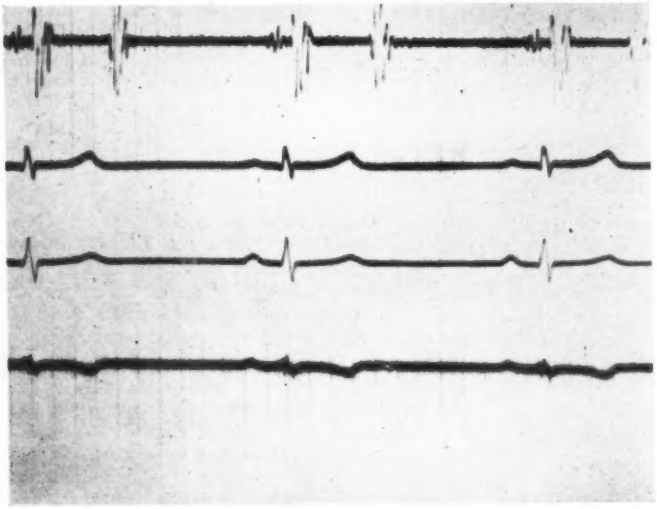

FIG. 2.—*Presystolic gallop rhythm.* The gallop sound coincides with the termination of the P wave in the electrocardiogram (three leads recorded simultaneously), and it is separated from the first sound by a silent interval.

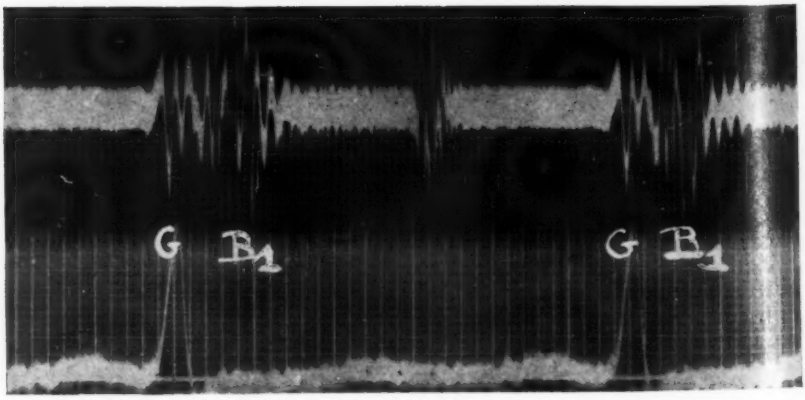

FIG. 3.—*Retarded presystolic gallop rhythm.* The gallop sound coincides with the termination of the P wave. There is no silent interval between the gallop sound and the first heart sound.

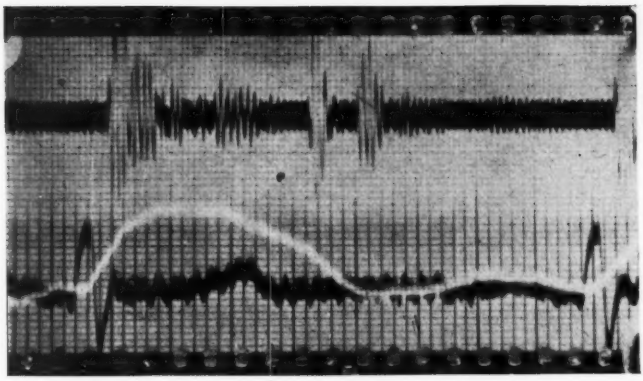

FIG. 4.—*Mitral opening snap.* Above, the phonocardiogram, below, in white, the apical electromyogram, and in black the electrocardiogram. The record shows, in succession, the first sound, a systolic murmur, the second sound, and finally the opening snap of the mitral. The second sound coincides with the start and the opening snap with the termination of the descending limb of the apical cardiogram. The snap begins 0·07 seconds after the start of the second sound.

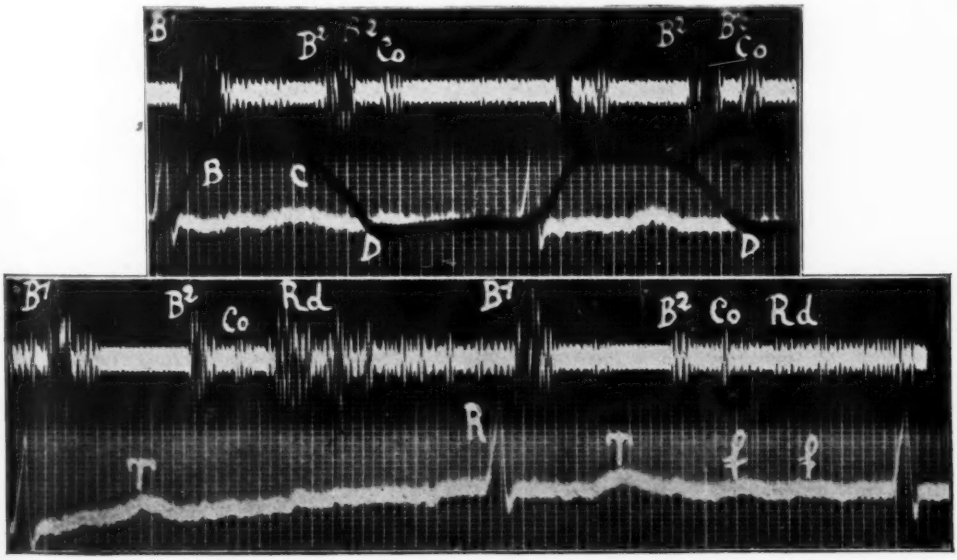

FIG. 5.—*The complete phonocardiogram of a case of mitral stenosis.*

(A) Above, phonocardiogram taken from the fourth left interspace, and below it, the apical electromyogram in black, and the electrocardiogram in white. These show the two elements of the reduplicated second sound which coincide with the start of the descending line CD of the apical cardiogram, then the mitral opening snap (CO), which coincides with the base of the descending line at D.

(B) Below phonocardiogram taken from the apex, in the left lateral decubitus. It shows successively the first sound, the second sound, the snap (CO) which is slight, and the diastolic rumble (Rd) with its initial protodiastolic accentuation. There is no presystolic accentuation owing to the presence of auricular fibrillation.

These two tracings were taken at the same time and from the same patient.

depends on an adhesion between the left pleura and the pericardium. In 10 per cent of such cases, there is also a *late systolic murmur* between the snap and the second sound. I have seen many cases in which the diagnosis of mitral stenosis was mistakenly made, simply on account of this late systolic snap, which is of no importance. The clinical recognition of this snap is not very difficult and with the phonocardiograph it is very easy.

The diagnosis between mitral triple rhythm and a *protodiastolic gallop* (Fig. 7) is not usually difficult as other signs of left ventricular failure accompany the gallop.

More difficult to distinguish from mitral triple rhythm is *the physiological third heart sound*, often heard in young subjects. It is usually intermittent. If it is permanent, the patient should be instructed to hold his breath after a deep inspiration, when the third heart sound will disappear immediately, a characteristic phenomenon.

Lastly, we must distinguish between mitral triple rhythm and the sign which I have described as *the isodiastolic or protodiastolic pericardial snap* (Fig. 8) of adhesive pericarditis. This sound is heard at the same site as the mitral opening snap but it is louder. When it is very loud, you may safely make the diagnosis of calcified pericardium.

In conclusion, I hope that I have shown you the great interest that attaches to phonocardiography in the study of triple heart rhythm.

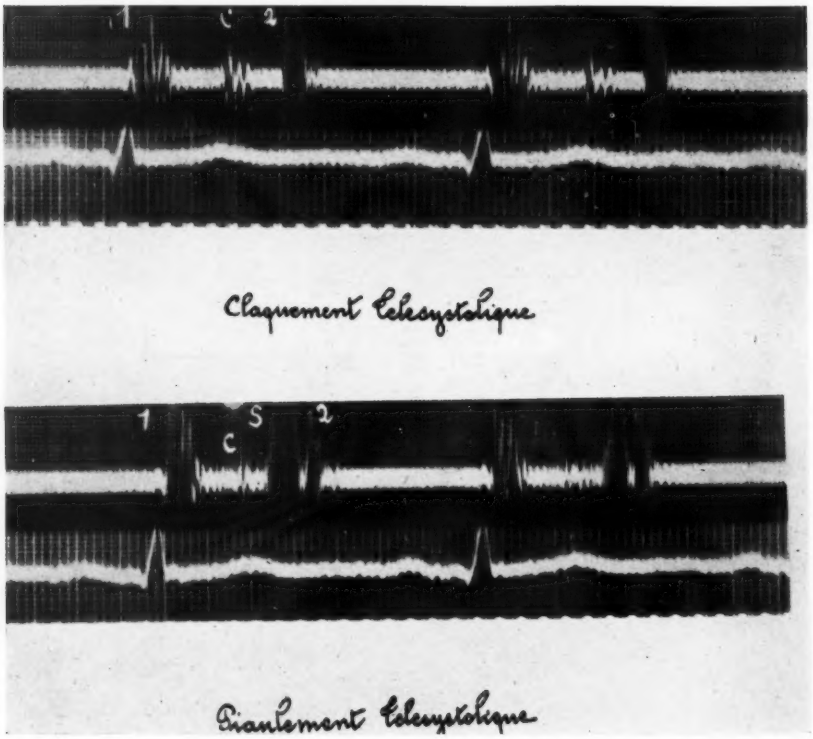

FIG. 6.—*Telesystolic snap and murmur* due to left-sided pleuro-pericardial adhesions. Above, the snap (C) situated between the first and second sounds, and nearer to the second. Below, the snap (C) is not pronounced, but the late systolic whining murmur is well shown between the snap and the second sound.

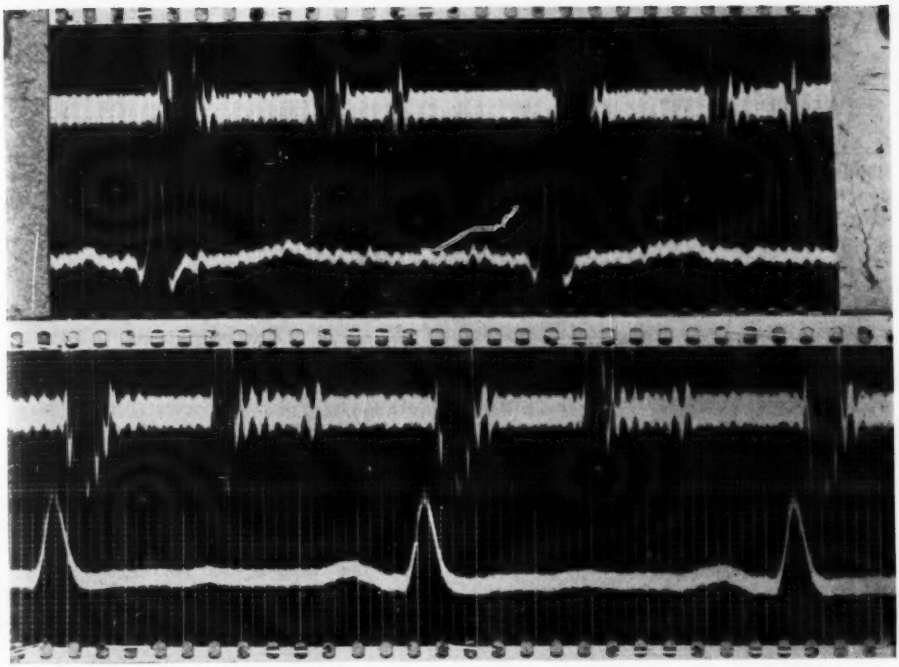

FIG. 7.—*Third heart sound and protodiastolic gallop.* Above, a third sound begins 0·13 seconds after the onset of the second sound. Below, a protodiastolic gallop sound begins 0·15 seconds after the onset of the second sound. The two records belong to different patients, but the phonocardiographic appearances are similar.

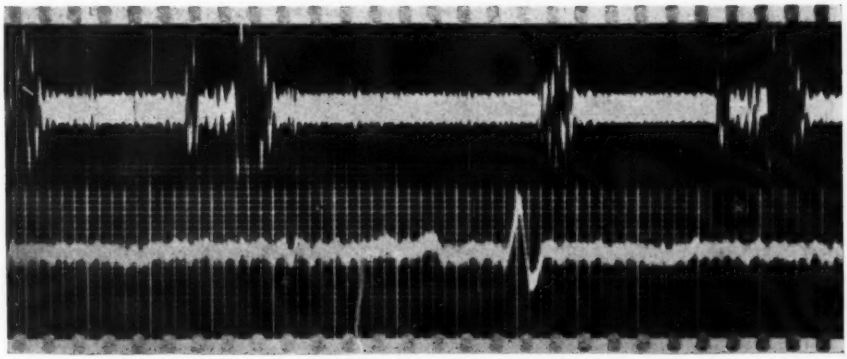

FIG. 8.—Intense *isodiastolic pericardial snap* (pericardial vibration) in a case of calcified pericardium. The snap occurs 0·08 seconds after the onset of the second sound, and is therefore isodiastolic. The vibrations are of far greater amplitude than those of the second sound.

Professor CRIGHTON BRAMWELL (Manchester) said how much he appreciated the privilege of hearing the communication of Professor Lian, an acknowledged master in this subject.

He then referred to certain difficulties which he himself had encountered in recording the heart sounds. In phonocardiography there were two distinct objectives. One was to obtain a true record of the heart sounds and murmurs, the other to determine their time relation to the events of the cardiac cycle. The second of these was relatively easy, but the first was much more difficult, because the sound picture was apt to be contaminated by instrumental artifacts. Wigger's optical method of recording heart sounds, employing a delicate rubber membrane and a very light mirror, was quite adequate for timing murmurs but did not give a true sound picture. Professor Bramwell showed a phonocardiogram taken from a patient with mitral stenosis and partial heart block. The murmurs in this case differed from cycle to cycle and would have been difficult to interpret without a graphic record. In cycles in which the P–R interval was prolonged the presystolic murmur died away before the first heart sound. When the ventricle failed to respond there was a loud murmur but no first sound, and in the cycles in which the P–R interval was normal there was no murmur. Clinically the reason for this was obscure but the record indicated that it was due to the fact that these cycles followed a missed beat. The auricle had already discharged its contents into the ventricle and when it contracted a second time the ventricle was already so full that the blood flow through the mitral orifice was not sufficient to produce a murmur.

He had used this method also for recording arterial sounds during deflation of the armlet in the estimation of blood pressure. These observations had revealed an important artifact, namely that if the pick-up is connected to the recorder by a tube, vibration of the air in the tube will distort the record. As in the case of an organ pipe, the frequency of vibration varies inversely with the length of the tube. This error is apt to contaminate all records in which air conduction is employed.

To obtain a true sound picture electrical conduction should be used since it is instantaneous. Further both pick-up and recorder must have a natural frequency higher than that of the vibrations which one wishes to record.

With this in mind he had used a Matthews' oscillograph in conjunction with a condenser microphone. Both these instruments have a natural period of over 10,000 a second which is well above the frequency of even the higher harmonics of the heart sounds. That this instrument does give a true sound picture is proved by the fact that the records are identical in form with those obtained with a cathode ray oscillograph which has no inertia. This apparatus is excellent for research purposes, but is somewhat temperamental, and it was only by having the collaboration of an expert physicist that he had been able to obtain consistently good results. For routine clinical work we want an instrument that is more fool-proof, like that of Lian and Minot or the Sanborn Stetho-cardiette.

Whereas the timing of heart sounds and murmurs by means of phonocardiography was easy, to obtain a true picture of the sound vibrations was more difficult, since the record was apt to be contaminated by instrumental artifacts. Both pick-up and recorder should have a natural frequency higher than that of the vibrations of the heart sounds and murmurs, and transmission should be by electrical and not by air conduction. For routine clinical work the instrument must be fool-proof.

SHORTER COMMUNICATIONS

September 12, 1947. Section of Cardiology

The Septal Anastomosis of the Coronary Arteries

By Prof. Laubry, Paris

No summary available

Repetitive Paroxysmal Tachycardia

By John Parkinson and Cornelio Papp, London

The name " repetitive " is here applied to a special variety of paroxysmal tachycardia in which brief paroxysms separated by sinus beats constantly recur over months or years.

Forty new cases of repetitive paroxysmal tachycardia have been collected, half of them with prolonged observation periods up to 18 years. Ages from 4 to 75 years with two-thirds of the patients (including seven children) under 40 years of age; males predominate. Of the 40 cases, only 3 had organic heart disease ; 2 gave a rheumatic history but had no heart disease; 3 had toxic goitre.

The usual symptom was palpitation, and four patients with ventricular paroxysms also had syncopal attacks. Fourteen patients, including seven children, were symptomless.

The only clinical sign was the peculiar irregular pulse.

Diagnosis was based on a particular kind of electrocardiogram recorded at numerous successive examinations. This almost always showed short paroxysms of tachycardia separated by normal sinus beats (paroxysmal tachycardia type), occasionally runs of multiform extrasystoles (extrasystolic type), more frequently both types together (mixed type).

The abnormal rhythm was divided as follows :

(a) Repetitive auricular paroxysmal tachycardia, 24 cases:—16 of the paroxysmal tachycardia type, 3 of the extrasystolic type, and 5 of the mixed type. The average rate was 150 in children and 130 in adults.

(b) Repetitive auricular *flutter*, 5 cases, 3 with irregular auricular rhythm (impure flutter), one with probable fibrillation.

(c) Repetitive *nodal* paroxysmal tachycardia, 2 cases.

(d) Repetitive *ventricular* paroxysmal tachycardia, 9 cases :—7 of the paroxysmal tachycardia type with normal beats separating the runs, 2 of the mixed type.

Repetitive paroxysmal tachycardia provides a connecting link between extrasystoles and paroxysmal tachycardia. The extrasystolic runs are always irregular and so are the shorter runs of paroxysmal tachycardia, but the longer runs of the latter type are as regular as ordinary paroxysmal tachycardia though somewhat lower in average rate.

This paroxysmal state is uncertain in its duration, but it often subsides. In children it may cease at adolescence; in adults it may last for years and then disappear as it did in 8 of 14 cases long observed. The prognosis as regards disability and length of life is good both in the auricular and ventricular form, though there are exceptions. Digitalis is rarely effective; quinidine occasionally controls the ventricular form. Repetitive paroxysmal tachycardia may be regarded as a distinctive disorder of rhythm rather than a cardiac disease of consequence.

Sympathectomy for Hypertension

By Geoffrey Bourne, London

Dr. Bourne said that he proposed to limit his remarks to the pathology of the condition and to try, from the information that was available, to stimulate a discussion as to whether sympathectomy was valuable, and at what stage of the disease it should be done.

The approach to that question had hitherto been very largely empirical; various observers had stated that in females from twenty to thirty the results were good, from thirty to forty not so good, and after fifty on the whole rather bad, but he felt that an attempt to decide this in terms of the numerical

years of a patient's life was unscientific because a man was as old as his arteries, and many people's arteries were very much younger than their years. There had been no real, comprehensible pathological basis explaining why it was that hypertension occurred. The only satisfactory experimental work had been that of Goldblatt, and the theories of hypertension had, since then, been very largely founded upon the renin hypothesis.

Within the last few months there had, however, emerged further work which might have considerable implications, and that was the work of Trueta and his colleagues at Oxford. They had been able to produce an experimental ischæmia in rabbits by stimulation of the nervous system; this ischæmia was one of the cortex of the kidney, and could be produced in the absence of any organic disease. It was possible that human hypertension in its early stages might be due to a similar phenomenon. Trueta and his colleagues had also shown that the same cortical blanching might be produced by various other means, some of them biochemical, and their second point was that synchronously with this cortical blanching of the kidney there was in fact developed a secondary renal circulation which allowed the blood to be short-circuited back into the kidney without ever having passed the cortex. This had been proved by injection methods and by seeing arterial blood pulsating in the renal vein during the course of their experiments on animals. They had found that animals did not all react in the same way, and also had some evidence that although the stimulus was largely through the nervous system it might be brought about by large doses of posterior pituitary extract.

During the early 'teens the boy or girl liable to hypertension had a blood pressure that was easily raised by emotion, but as the years went by there was a more permanent increase in the systolic and diastolic figures, and round about the age of forty there was developed the clinical case of persistent hypertension. In the earlier stages there was a possibility of reducing the raised blood pressure temporarily to normal by the use of sedatives or by rest in bed or starvation, and many of the other means that had been employed hitherto in the treatment of hypertension, but after a variable time the factor of arterial degeneration was superimposed, so that in addition to spasm the hypertension was partially due to organic vascular renal disease. Cortical spasm alone might well be the actual cause of hypertension in the younger, and a mixture of spasm and permanent renal disease in the older group.

He described one similar to many hundreds seen by others, of a man of 37 years of age who, at 15 and at 17, had been examined and found to have high blood pressure; and at 22 they had the first recorded figures, 240/160: at the age of 32 it was 180/140 and at 37, 194/124, so that for over twenty years he had had considerable hypertension without any shortage of breath, or headaches, or any symptoms whatever. He thought he might make quite legitimate deductions from such cases: the first was that long-sustained increased pressure as such had no effect deleteriously on either the arteries or on the heart, hypertrophy only being caused. During this first stage of hypertension there was available post-mortem evidence from young subjects, whose arteries had been examined, no sign whatever of any degeneration being apparent, such cases having been knocked down in the street or having died of something else.

In the second stage one began to get arterial degeneration, and it seemed clear that this degeneration was really the first and primary cause of the so-called hypertensive lesions in heart, kidney, or retina. Such degeneration in most cases was a manifestation of age, or wear and tear, but in a few young subjects the arterial tissue was affected by the presence of chronic nephritis.

When it came to consideration of the effects of sympathectomy cases seemed to be divided into two kinds: in one case the operation succeeded, and in another it clearly failed—there being a temporary fall in the blood pressure which within three months or so had risen again.

It was clear they did not want to use sympathectomy too early, because such a patient might easily live without symptoms for twenty years with hypertension. The actual follow-up of all cases of sympathectomy did not extend farther back than something like eight years. If sympathectomy were done at this early stage it would be less easily applicable later when its help might be needed by the patient because of the onset of advancing arterial disease. If a second sympathectomy were then done it certainly would be much more difficult technically. Sympathectomy was equally contraindicated when dealing with cases that had severe or advanced vascular disease, particularly of the kidneys. It would therefore seem to be their duty to try to find some way of judging when a patient was approaching the end of his period of benign hypertension, and not to leave it too late before they decided that sympathectomy should be done. There were, of course, exceptions to the rule, such as those cases of malignant hypertension, particularly in young subjects with advanced retinitis who could barely see, but after operation could read. The charts and retinal pictures of two such cases were shown, who during the post-operative five and six months

had improved greatly, both as regards vision and as regards general health.

The family history was also helpful: there were those individuals who had in the family a number of relations who had had raised blood pressure for many years without symptoms, and on the contrary there were families, many of whom seemed to die at the age of about forty-five. Probably the safest guide was a regular periodic and careful examination of the patient, so that one might soon become aware early of any fresh change that had started to occur. A watch should be kept for a sudden increase in the already high blood pressure and close observation of the retina should be made periodically by the same ophthalmic surgeon. Then again, obvious deterioration in the cardiac function, as shown by increasing size of the heart and increasing shortness of breath would immediately lead one to consider most carefully whether sympathectomy should or should not be done. In such cases angina and coronary disease were a contraindication to sympathectomy. The renal function should be similarly reassessed at intervals. Evidence of definite impairment of this was also a contraindication to the operation.

By Sven Hammarström, St. Erik's Hospital, Stockholm

The neurosurgical treatment of hypertension was introduced in Sweden in 1940 by Olivecrona and Berglund. I have followed up 100 of their patients one to seven years after sympathectomy (*Acta med. Scand.*, 1947, Suppl. 192). Most of the patients were submitted to dorso-lumbar sympathectomy according to Smithwick and a smaller group to supradiaphragmatic sympathectomy according to Peet. The results of the last mentioned one-stage operation on the whole agree with those obtained with the more complicated and extensive method. I recommend Peets' operation in selected cases of less severe hypertensive disease.

About one half of the patients in our series before operation had a severe hypertensive disease with retinal exudates and hæmorrhages. The operative mortality was 2 per cent and the late mortality 20 per cent.

Even under so-called basal conditions there is a great variability of blood pressure in all groups of hypertensive patients, which must be considered in the evaluation of the effect of sympathectomy. I have studied the blood pressure before and at various lengths of time after sympathectomy by means of 24-hour readings, which made possible a statistical evaluation of the significance of the post-operative change. In 60 per cent of the patients still alive there is a significant drop in systolic and diastolic pressure during the whole follow-up time. This lowering was regularly followed by an improvement or complete disappearance of hypertensive retinopathy and improvement or return to normal of the electrocardiogram.

In 50 patients the average post-operative drop in systolic and diastolic pressure was essentially the same according to 24-hour readings registered shortly after the operation and after an average time of three years. Furthermore the average drop in blood pressure was the same in those examined shorter and longer time than three years after sympathectomy.

Contrary to the long-standing lowering of blood pressure in the recumbent position, the post-operative orthostatic hypotension and tachycardia is transient. Repeated tilting tests after sympathectomy showed that the orthostatic changes gradually subsided and usually disappeared within one year after sympathectomy. There is furthermore no correlation between the amount of the pressure lowering in the recumbent position and the degree of the orthostatic changes.

There is still no reliable test to predict the effect of sympathectomy. I found no correlation between the postoperative change in blood pressure and its height, or spontaneous or induced variability before operation. The main indication for sympathectomy is a progressive hypertensive disease with retinopathy, left ventricular strain, and cerebral symptoms, in the absence of the signs of severe organic vascular damage, which will be described below. We do not usually operate on patients with uncomplicated hypertension who show no other objective signs than elevated pressure or in addition left axis deviation in the cardiogram and/or slight vascular eye-ground changes. These patients, who constitute the great majority, often have a transient hypertension and only a slight excess mortality compared with the average population (Bechgaard (1946), *Acta med. Scand.*, Suppl. 172). The occurrence and degree of subjective symptoms in hypertensive disease does not run parallel with the objective signs. Even in benign hypertension the subjective symptoms may be incapacitating. In most of these patients medical and psychotherapeutical measures give adequate relief. In those who are unimproved by such prolonged treatment sympathectomy is advisable on account of its striking effect on headache and other subjective symptoms with restitution of the working capacity.

An analysis of the failures of sympathectomy in our series showed that the following signs contraindicated neurosurgical treatment. Impaired renal function shown by more than one of the following signs: albuminuria, non-protein nitrogen above 45 mg. per 100 ml., creatinine clearance below 80 ml./minute, cardiac decompensation where less than ordinary activity causes discomfort, and enlargement of the heart volume above 500 ml/m² body surface. Valvular lesions and coarctation of the aorta must also be excluded. Cerebral lesions with persistent symptoms such as hemiplegia or even advanced hypertensive encephalopathy contraindicate sympathectomy.

Tomography in the Study of the Cardiovascular System

By E. Tiscenco and J. H. Wright, Glasgow

An attempt was made to illustrate the application of tomography of the cardiovascular system by lantern slide demonstration. In the absence of the apparatus for tomographic screening, a procedure was suggested by which the accuracy of the tomographic positioning, particularly for oblique projections, can be enhanced.

The pulmonary vascular structures in health and in emphysema were demonstrated.

The various parts of the normal aorta were shown followed by the appearances of the aorta in atheroma and in aneurysms.

The normal left atrium was displayed by a tomographic section and compared with the appearances in varying degrees of its enlargement. When straight examinations are inconclusive tomography may be of diagnostic value.

The outflow and inflow tracts of the right ventricle were tomographically defined. Examples of eccentric and concentric hypertrophy of the left ventricle in hypertension were given.

A structure seen in several tomographs, substantiated by anatomical comparison as well as by demonstration of the lobus venæ azygos, was shown to be consistent with the major azygos vein.

The last section of the demonstration was confined to the differentiation of pathological shadows projected close to or into the cardiovascular structures.

Although the study was not conclusive, it was hoped that improvement in the mechanical side of tomography would not only enhance its accuracy but fully justify its application in the study of cardiovascular radiology.

RAPID DIGITALIZATION

BY

WILLIAM EVANS, PETER DICK,* AND BYRON EVANS

From the Cardiac Department of the London Hospital

Received February 14, 1948

When it has been decided to give digitalis to a patient with heart failure, the need for inducing its effects quickly (rapid digitalization) is sometimes evident. There is no unanimity on the best preparation to use for this purpose nor on the best way to give the preparation of choice. Mackenzie (1914) said that he seldom failed to induce rapid digitalis effect by giving the drug by mouth, but occasionally in auricular fibrillation when the heart rate exceeded 140 a minute he had found that strophanthin (1/125 grain) intravenously reduced the rate and relieved symptoms in five to eight hours. From his own observation he saw no reason to give preference to any preparation, but he pointed out the need to investigate this problem. In 1925 Cushny again stressed the necessity to examine the comparative value of digitalis preparations.

There is available a comparison of series of patients on different drugs with a digitalis effect, but the relative value of two or three preparations in the same patient has seldom been reported. The present clinical trial was designed to discover the most effective preparation for rapid digitalization when given orally or intravenously, by comparing the effect of as many preparations as possible in the same patient and under the same conditions. This procedure does not appear to have been adopted for rapid digitalization as it has been done in the case of maintenance therapy (Evans, 1940).

It was decided to test the following drugs as likely to prove of value: strophanthin, ouabain and k-strophanthosid, digoxin, digitoxin, lanatoside C, digitalis leaf, and the tincture of digitalis. In addition, certain remedies like coramine and cardiazol were given to certain cases as a control. In order that the results might be comparable it was necessary to give a full dose of each drug. In the earlier cases varying doses of some preparations were tried and in certain instances doses considerably larger than those recommended were used. The relative value of these preparations was studied in 20 patients.

The most satisfactory index of digitalization is the fall in the ventricular rate in auricular fibrillation and this was used, but improvement in the objective signs of failure was also observed and so was the diuretic response. Because no digitalis preparation was to be given between the testing of each individual preparation, cases with severe heart failure could not be used. Cases of rapid auricular fibrillation with slight or moderate congestive heart failure, were selected. The patients had mitral stenosis, occasionally combined with aortic incompetence, or had hypertension. They were confined to bed on a normal hospital diet and fluids were restricted. The fluid intake and urinary output were measured. The apical rate was particularly recorded and any change in the signs of heart failure was looked for. The majority received no other treatment, apart from sedatives when necessary, but in a few with moderate œdema mercurial diuretics were not withheld; they were not given during the testing period for the separate digitalis preparations nor on the preceding day. After a few days of preliminary observation, and after ensuring that no digitalis had been given during the previous seven days, the first preparation was given. The apical rate was counted over three consecutive half minutes; the respiration and blood pressure were also noted. The drug was then given, and the heart rate was counted for three consecutive half-minute periods every quarter of an hour, until it had ceased to fall over a period of one and a half to two hours. It was found in practice that the fall was almost always complete within four hours. Symptoms and signs of toxicity were sought. Subjective and objective signs of improvement were noted during the following forty-eight hours although a noticeable change was not found because of the relative freedom from symptoms

* This work formed the basis of a thesis submitted by P.D. and accepted for the M.D. Degree of the University of Cambridge.

shown by the selected cases while at rest in bed. A conspicuous diuretic response seldom resulted in these patients with only slight heart failure, and it was too erratic to be accepted as a measure of the benefit. Reliance was placed on the heart rate as a criterion of improvement in the selected cases, during a short period following the administration of a particular digitalis preparation.

The following is an example of how each trial was recorded.

Name : C. J. S. *Age :* 31. *Date :* 22/11/45.
Diagnosis and Summary : Mitral stenosis, auricular fibrillation, and heart failure.
Observation : Effect of 3 mg. digoxin given orally.

Time	Ventricular rate	Respiratory rate	Blood pressure	Remarks
10.30 a.m.	140.134.146		120/80	
10.45 a.m.	142.130.130	18		Digoxin 3·0 mg. given orally.
11.0 a.m.	114.128.126			
11.15 a.m.	124.130.132		115/70	
11.30 a.m.	140.138.124			
11.45 a.m.	116.116.116	16		
12.0 p.m.	130.120.116			
12.15 p.m.	104.108.108		110/75	Had dinner 12.20 p.m. Onset of nausea; unable to eat pudding.
12.30 p.m.	120.110.110			Very nauseated.
12.45 p.m.	116.106.110	14		Nausea less.
1.0 p.m.	118. 98.106			Nausea completely gone.
1.15 p.m.	98. 98.106		110/70	
1.30 p.m.	100. 88. 94			
1.45 p.m.	96. 92. 92	14		
2.0 p.m.	104. 86. 92			
2.15 p.m.	84. 80. 84		110/75	
2.30 p.m.	86. 84. 92			
2.45 p.m.	82. 76. 74	14		
3.0 p.m.	74. 80. 76			
3.15 p.m.	74. 84. 80		110/75	
3.30 p.m.	76. 74. 74			
3.45 p.m.				
4.0 p.m.	74. 80. 94			
4.15 p.m.	86. 86. 84		120/80	
4.30 p.m.	80. 80. 88			
4.45 p.m.	78. 80. 82			
5.0 p.m.	88. 84. 80			
5.15 p.m.	80. 84. 78			
5.30 p.m.	80. 78. 76			
6.0 p.m.	76. 80. 80			
8.0 p.m.	80. 84. 80			
23.11.45				
8 a.m.	74. 72. 68			No diuresis took place.

The patient received no further digitalis for a period of three to fourteen days, until the ventricular rate had returned to its previous level and the effects of the previous preparation had worn off. The length of time varied with the different preparations. On many occasions the ventricular rate did not return exactly to its previous rate, tending to settle at a lower level after a trial with each preparation. This experimental error, with a variation between the first and second preparation greater than between succeeding preparations, was never great, and was partly overcome by giving the preparations in a different order to each patient, a practice always adopted. The number of tests that it was possible to carry out in each case was thus limited by the failure of the ventricular rate to rise to a comparable level after a variable number of tests. In several cases after the first preparation it did not rise sufficiently for a fair comparison to be made with succeeding preparations and such were excluded from the series. For this reason it proved difficult to collect a series of suitable patients for this investigation.

Results

The criterion adopted for the effectiveness of a preparation has been the fall in heart rate produced

by it. The results are summarized in the form of graphs showing this fall in heart rate. The fall shown at each time period is an average of the preceding half-hour or hour's readings, deducted from the average initial rate before the administration of the drug, and thus represents the effect of the drug during the preceding half-hour or hour. They are arranged usually in the order of effectiveness, and not in the order the drugs were given, for this was deliberately varied.

The extent of the fall in heart rate produced by a digitalis preparation has been shown to be closely related to the initial heart rate (Lyon and Gilchrist, 1927), as would be expected. The tendency of the heart rate to fall throughout the periods of trial in most cases, coinciding with the improvement of heart failure, has already been mentioned. It is seldom possible to simulate laboratory conditions in a clinical investigation, and it could not be anticipated that any patient would be in exactly the same state prior to the administration of each preparation. The consistency of action of a drug in the same dosage and in the same patient was tested in two cases. In one case, receiving 1·5 mg. of digoxin by mouth on two occasions with a week's interval, although the initial heart rate was almost identical in both trials, the effect was different whereas in another case the effect was almost identical (Fig. 1). On the whole drugs were found to reproduce the same result with remarkable consistency in successive cases.

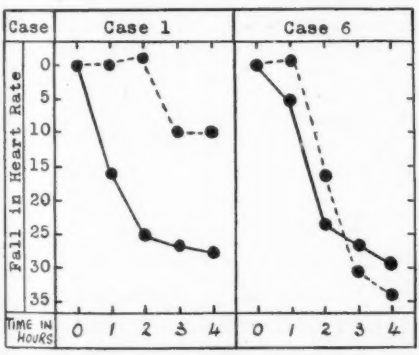

FIG. 1.—Comparing the effects of repeated digitalis medication in the same patient. In Case 1 the effect of 1·5 mg. of digoxin by mouth was not the same, but in Case 6 the effect of 2·0 mg. of digoxin by mouth was identical on each occasion. Continuous and discontinuous lines represent separate trials with one week's interval.

A further difficulty was the determination of the size of the dose for each patient. The amount that will produce a full digitalis effect is known to vary a great deal in different patients, a fact that was apparent in these trials. With the lesser doses, unless a satisfactory therapeutic action had taken place, there was no certainty that the patient had received what was for him a full dose of that preparation, and the result could not, therefore, be fairly compared with the action of another preparation. For the purpose of comparison of the different drugs, a minimum full dose was chosen for each preparation, based partly on the result of these trials and partly on previous experience. A further difficulty was the variability in the time taken to induce proper digitalization in relation to the size of the dose when given by mouth. With large doses, such as 3 mg. of digoxin by mouth, an effect was seen more rapidly than with smaller doses, although the final effect might be the same. It was occasionally noticed with oral administration that the full effect was not seen within four hours, so that when comparing two drugs the results observed within four hours might reflect the dosage rather than the effectiveness of the preparation. With intravenous therapy the maximal effect was invariably seen within four hours and comparison with an oral preparation might on that account be open to the same fallacy at times.

As this study was undertaken to ascertain the best preparations for rapid digitalization some time-

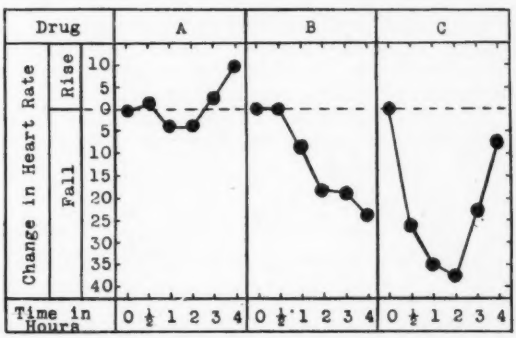

FIG. 2.—Rapid digitalization in a man aged 60 with hypertension and auricular fibrillation. (A) Digitaline (Nativelle), 2·0 mg. by mouth. (B) Digoxin, 2·0 mg. by mouth. (C) K-Strophanthosid, 0·5 mg. intravenously.

limit had to be applied within which the effect would be regarded as rapid. Four hours was selected as a suitable period for it represents the time which may be regarded as maximal in a patient requiring rapid digitalization. The comparison of results, therefore, has been based entirely on a preparation's effectiveness within that period.

In giving the results each drug is considered in turn and its effectiveness judged in each patient. A digitalis effect was classified as good when the fall in heart rate within four hours was 75 per cent of the maximal fall produced by any preparation in that patient, moderate between 50 and 75 per cent, and slight below 50 per cent. This method of assessing the therapeutic effect was possible, as an optimum result was produced in all patients, with the exception of one, by at least one preparation. The results are summarized in the form of a Table for each drug, showing the number of times it was more, equally, or less effective than the others, within two and within four hours. The effect of two preparations was regarded as equal if the difference in the fall of the heart rate was not more than 5 per cent of the maximum produced by any drug in that patient. Tables 1 to 7 show the number of times each preparation proved more effective than the other, but they do not show the relative differences. Table 8 shows the consistency of effectiveness of each drug in different doses. The actual change in the heart rate from different preparations in the same patient is shown in Fig. 2 to 20.

Other remedies. These were introduced solely for the purpose of controlling the results obtained from the use of active preparations.

Coramine (Nikethamidum B.P.), described as a respiratory and vasomotor stimulant, was given once in a dose of 1·7 ml. and four times in a dose of 3·4 ml. of a 25 per cent solution intravenously. In one case its administration was followed by momentary dizziness, but no other effect was noted and there was no significant change in the heart rate.

Cardiozol (Leptazolum B.P.), a convulsant in large doses, and stated to be a respiratory and vasomotor stimulant in smaller doses, was given to two cases in a dose of 2 ml. intravenously. In one case the rate rose from 100 to 105 during the first five minutes and remained at about this level for the first hour, but during the second hour it averaged 125. In another the injection was followed by a sensation of dizziness lasting eight minutes. The heart rate rose from 105 to 140.

Analeptic preparation 3067/16 (Roche) was given intravenously once. Two minutes later the patient experienced severe dizziness and mental excitement which passed off gradually. A slight rise in the heart rate took place.

Cycliton was given once in a dose of 2 ml. intravenously. The heart rate rose sharply following the injection.

Strophanthin

Strophanthin was given intravenously 6 times in a dose of 1/100 gr. (0·65 g.) and 4 times in a dose of 1/60 gr. (1·08 mg.). In a dose of 1/100 gr. it had a good effect once, a slight effect once, and practically none in another. In two cases a sharp fall in the heart rate occurred during the first hour, but it had risen to its previous level by the fourth hour. In one case it was followed by a slight rise in rate. In a dose of 1/60 gr. it had a good effect three times, and a slight effect once. No toxic effects were seen. From previous reports 0·5 mg. is generally regarded as the maximal safe dose, and this, therefore, was considered to be a full dose for the purpose of comparison. It was compared with ouabain intravenously 3 times, strophosid intravenously 3 times, digalen intravenously twice, digoxin by mouth 14 times, digoxin intravenously 10 times, digitaline (Nativelle) by mouth once, and lanatoside C intravenously 3 times. The results are shown in Table I.

TABLE I

THE EFFECT OF STROPHANTHIN INTRAVENOUSLY COMPARED WITH THAT OF OTHER PREPARATIONS

Drug for comparison	No. of trials	Efficiency of Strophanthin compared with other Preparations					
		Within 2 hours			Within 4 hours		
		Greater	Equal	Less	Greater	Equal	Less
Ouabain	3	3	—	—	2	1	—
Strophosid	3	—	1	2	—	1	2
Digalen	2	1	—	1	1	—	1
Digitaline (Nativelle) (m) ..	1	1	—	—	—	—	1
Digoxin (m)	14	6	1	7	2	—	12
Digoxin (v)	10	1	1	8	—	1	9
Lanatoside C (v)	3	—	1	2	1	—	2

In this and in other tables (m) indicates that the preparation was given by mouth and (v) intravenously.

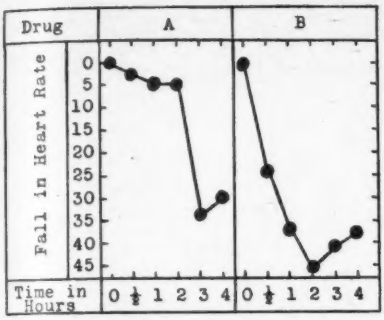

FIG. 3.—Rapid digitalization in a woman aged 61 with mitral stenosis and auricular fibrillation. (A) Digitaline (Nativelle), 1·75 mg. by mouth. (B) Lanatoside C, 1·2 mg. intravenously.

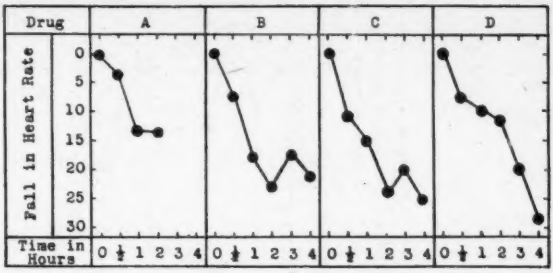

FIG. 4.—Rapid digitalization in a man aged 54 with hypertension and auricular fibrillation. (A) Digoxin, 1·5 mg. by mouth. (B) Digoxin, 1·5 mg. intravenously. (C) Lanatoside C, 1·5 mg. intravenously. (D) Digitaline (Nativelle), 1·2 mg. intravenously.

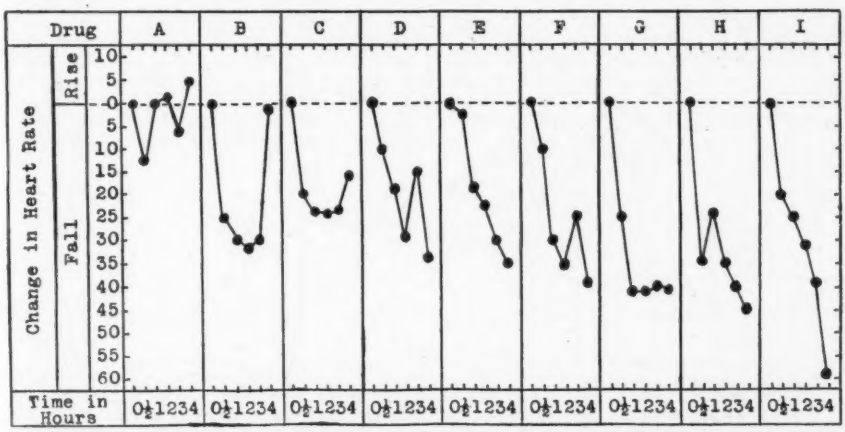

FIG. 5.—Rapid digitalization in a woman with mitral stenosis and auricular fibrillation. (A) Coramine, 3·4 ml. intravenously. (B) Lanatoside C, 1·0 mg. by mouth. (C) Lanatoside C, 1 mg. intravenously. (D) K-Strophanthosid, 1 ml. intravenously. (E) Strophanthin, 1/60 gr. intravenously. (F) Digoxin, 2·0 mg. by mouth. (G) Digoxin, 1·5 mg. intravenously. (H) Digalen, 1 ml. intravenously. (I) Digoxin, 3·0 mg. by mouth.

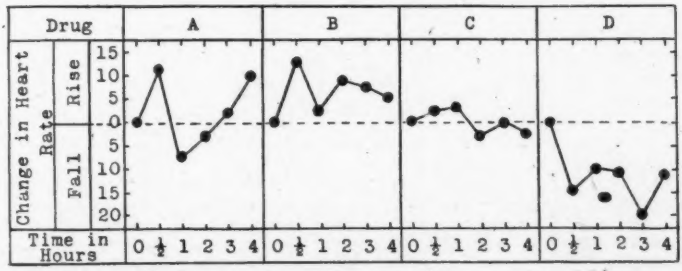

FIG. 6.—Rapid digitalization in a man with hypertension and auricular fibrillation. (A) Analeptic 3067/16 (Roche), 2 ampoules intravenously. (B) Cardiazol, 2 ml. intravenously. (C) Coramine, 3·4 ml. intravenously. (D) Tincture of digitalis, 2 drachms by mouth.

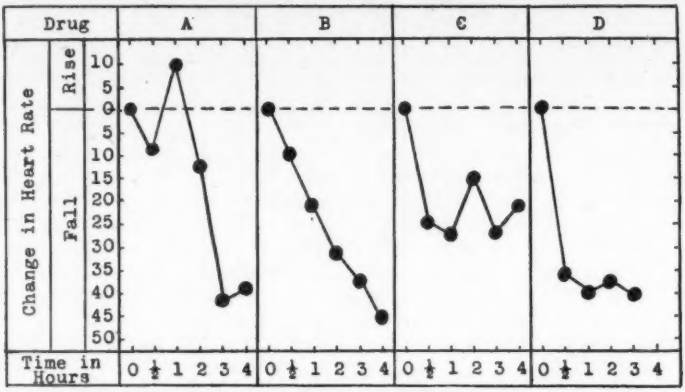

FIG. 7.—Rapid digitalization in a woman aged 37 with mitral stenosis and auricular fibrillation. (A) Digoxin, 1·5 mg. by mouth. (B) Digitaline (Nativelle), 2·0 mg. by mouth. (C) Lanatoside C, 3·0 mg. by mouth. (D) K-Strophanthosid, 0·5 mg. intravenously.

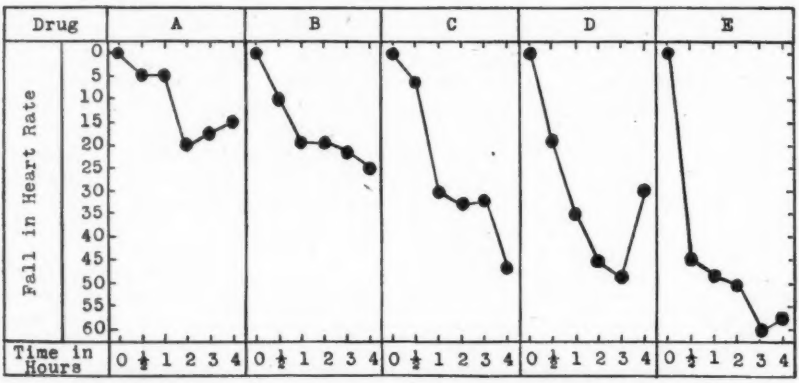

FIG. 8.—Rapid digitalization in a woman aged 57 with hypertension and auricular fibrillation. (A) Digitaline (Nativelle), 1·25 mg. by mouth. (B) Digoxin, 1·25 mg. by mouth. (C) Digitaline (Nativelle), 1·2 mg. intravenously. (D) Digoxin, 1·25 mg. intravenously. (E) Lanatoside C, 1·5 mg. intravenously.

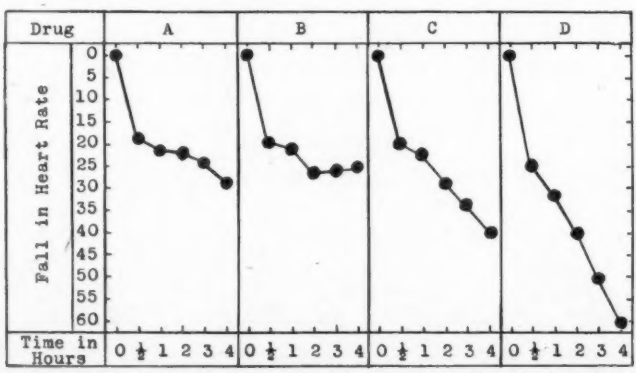

FIG. 9.—Rapid digitalization in a woman aged 48 with mitral stenosis, aortic incompetence, and auricular fibrillation. (A) Digoxin, 1·5 mg. intravenously. (B) Digitaline (Nativelle), 1·5 mg. intravenously. (C) Digitaline (Nativelle), 1·5 mg. by mouth. (D) Lanatoside C, 1·5 mg. intravenously.

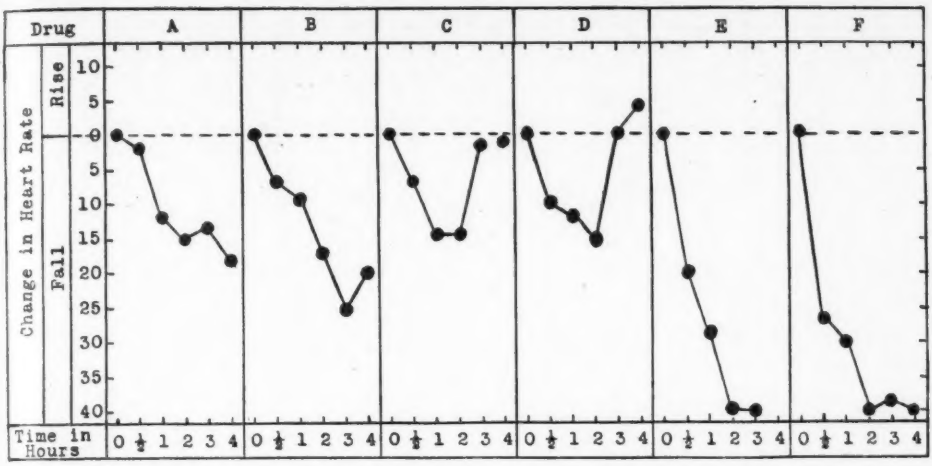

FIG. 10.—Rapid digitalization in a man aged 29 with mitral stenosis and auricular fibrillation. (A) K-Strophanthosid, 0·5 mg. intravenously. (B) Digitaline (Nativelle), 2·0 mg. by mouth. (C) Digoxin, 2·0 mg. by mouth. (D) Lanatoside C, 3·0 mg. by mouth. (E) Lanatoside C, 1·5 mg. intravenously. (F) Digitaline (Nativelle), 1·5 mg. intravenously.

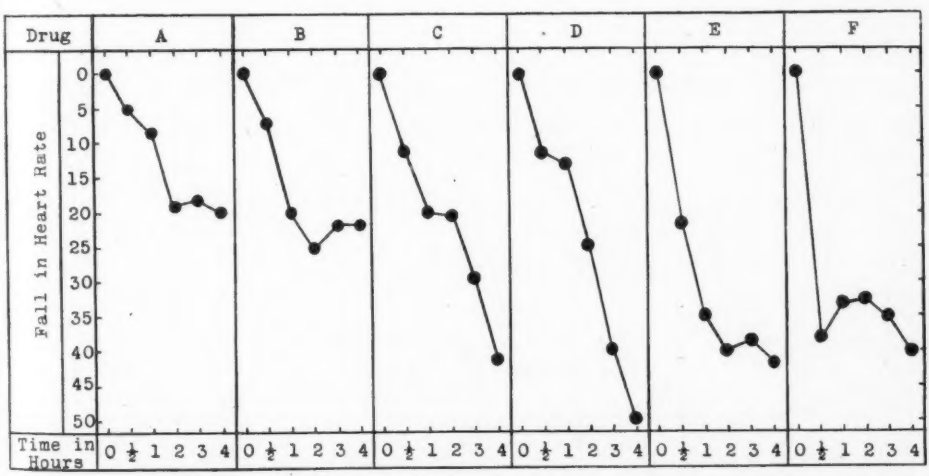

FIG. 11.—Rapid digitalization in a man aged 31 with mitral stenosis and auricular fibrillation. (A) Lanatoside C, 3·0 mg. by mouth. (B) K-Strophanthosid, 0·5 mg. intravenously. (C) Digitaline (Nativelle), 2·0 mg. by mouth. (D) Digoxin, 3·0 mg. by mouth. (E) Digitaline (Nativelle), 1·5 mg. intravenously. (F) Lanatoside C, 1·5 mg. intravenously.

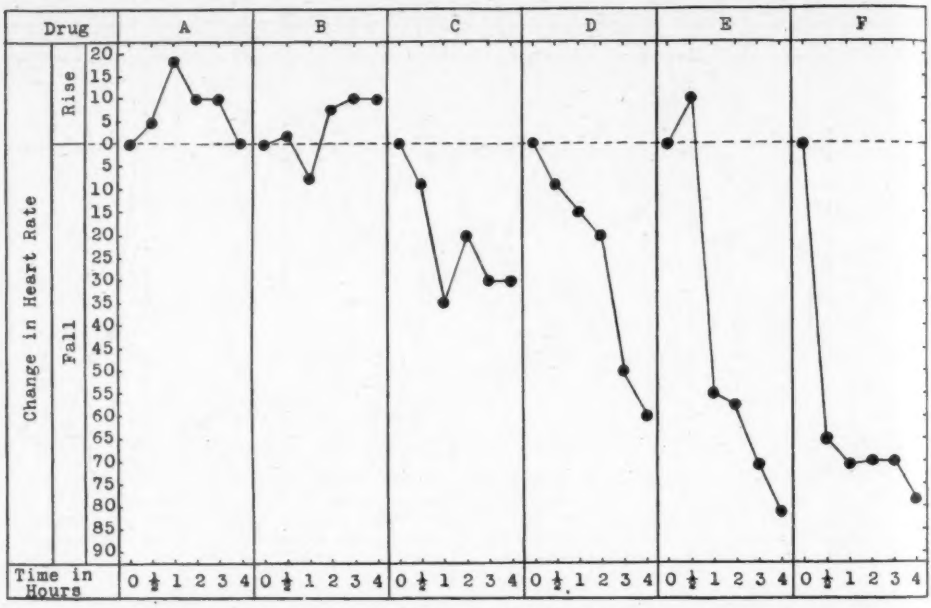

FIG. 12.—Rapid digitalization in a woman aged 34 with mitral stenosis and auricular fibrillation. (A) Lanatoside C, 3·0 mg. by mouth. (B) Coramine, 1·7 ml. intravenously. (C) Lanatoside C, 0·8 mg. intravenously. (D) K-Strophanthosid, 1 ml. intravenously. (E) Digoxin, 3·0 mg. by mouth. (F) Digoxin 1·5 mg. intravenously.

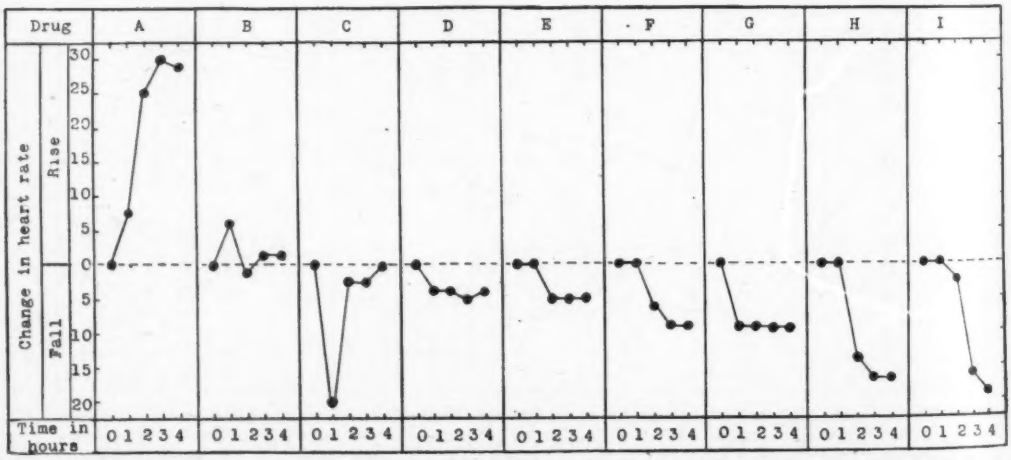

FIG. 13.—Rapid digitalization in a man aged 45 with mitral stenosis and auricular fibrillation. (A) Cardiazol, 2 ml. intravenously. (B) Ouabain, 1/240 gr. intravenously. (C) Strophanthin, 1/100 gr. intravenously. (D) Coramine, 3·4 ml. intravenously. (E) Strophanthin, 1/60 gr. intravenously. (F) Digoxin, 1·5 mg. by mouth. (G) Digoxin, 1·0 mg. intravenously. (H) Digoxin 1·5 mg. chewed. (I) Digoxin, 3·0 mg. by mouth.

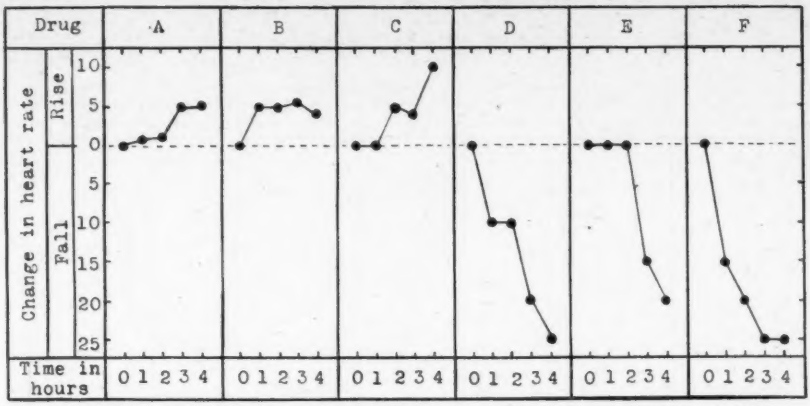

FIG. 14.—Rapid digitalization in a man aged 54 with hypertension and auricular fibrillation. (A) Digitalis leaf, 6 grains by mouth. (B) Tincture of digitalis, 2 drachms by mouth. (C) Digitaline (Allen and Hanbury), 1/30 gr. by mouth. (D) Strophanthin, 1/100 gr. intravenously. (E) Digoxin, 1·5 mg. by mouth. (F) Digoxin, 1·0 mg. intravenously.

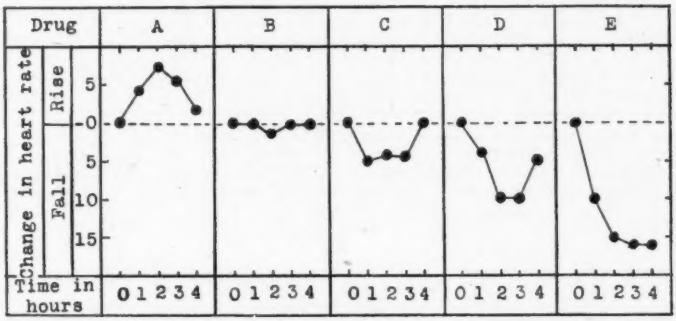

FIG. 15.—Rapid digitalization in a man aged 61 with hypertension and auricular fibrillation. (A) Strophanthin, 1/100 gr. intravenously. (B) Digitaline (Allen and Hanbury), 1/30 gr. by mouth. (C) Digoxin, 1·5 mg. by mouth. (D) Digitalis leaf, 6 gr. by mouth. (E) Digoxin, 1·0 mg. intravenously.

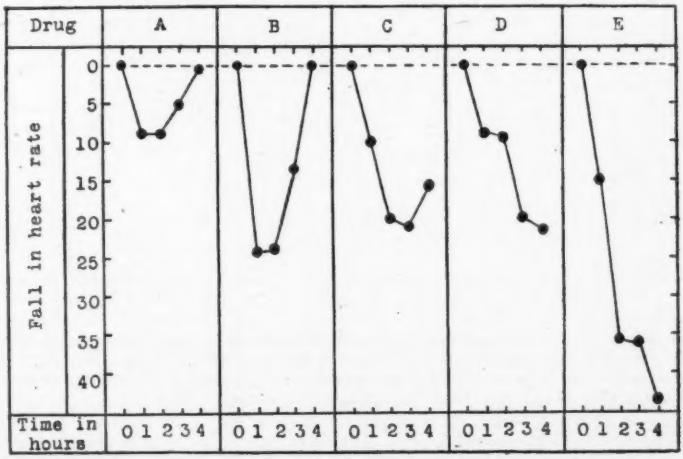

FIG. 16.—Rapid digitalization in a woman aged 31 with mitral stenosis and auricular fibrillation. (A) Digitaline (Nativelle), 1/300 gr. intravenously. (B) Strophanthin, 1/100 gr. intravenously. (C) Digitaline (Nativelle), 1/50 gr. by mouth. (D) Digoxin, 1/5 mg. by mouth. (E) Digoxin, 1·5 mg. intravenously.

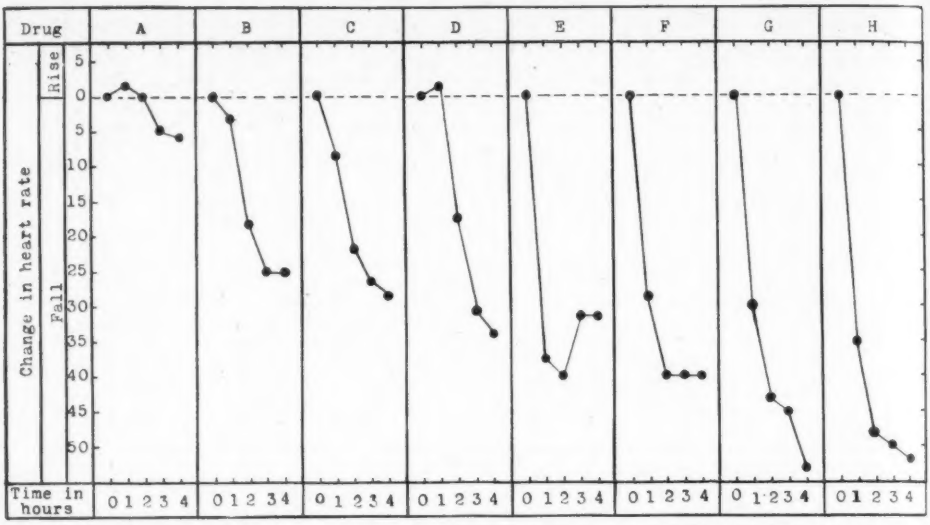

FIG. 17.—Rapid digitalization in a woman with mitral stenosis and auricular fibrillation. (A) Coramine, 3·4 ml. intravenously. (B) Digoxin, 1·0 mg. by mouth. (C) Digoxin, 2·0 mg. by mouth. (D) Digoxin, 2·0 mg. by mouth. (E) Strophanthin, 1/60 gr. intravenously. (F) Digoxin, 1·0 mg. intravenously. (G) Lanatoside C, 0·8 mg. intravenously. (H) K-Strophanthosid, 1 ml. intravenously.

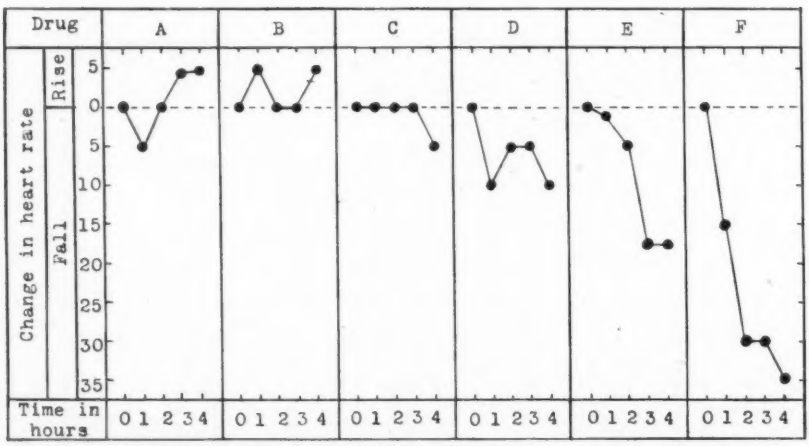

FIG. 18.—Rapid digitalization in a man aged 46 with mitral stenosis and auricular fibrillation. (A) Digitaline (Allen and Hanbury), 1/30 gr. by mouth. (B) Tincture of digitalis, 2 drachms by mouth. (C) Digitalis leaf, 6 gr. by mouth. (D) Strophanthin, 1/100 gr. intravenously. (E) Digoxin, 1·5 mg. by mouth. (F) Digoxin, 1·0 mg. intravenously.

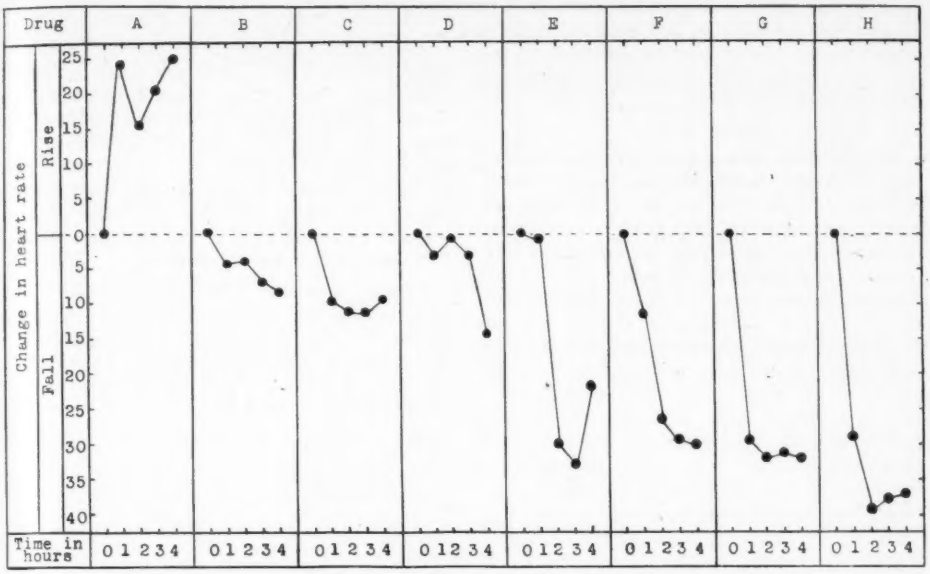

FIG. 19.—Rapid digitalization in a woman aged 76 with mitral stenosis and auricular fibrillation. (A) Cycliton, 2 ml. intravenously. (B) Digitaline (Nativelle), 1/240 gr. intramuscularly. (C) Ouabain, 1/240 gr. intravenously. (D) Digalen, 1 ml. intravenously. (E) Digoxin, 1 mg. intravenously. (F) Strophanthin, 1/60 gr. intravenously. (G) Lanatoside C, 4 ml. intravenously. (H) K-Strophanthosid, 1 ml. intravenously.

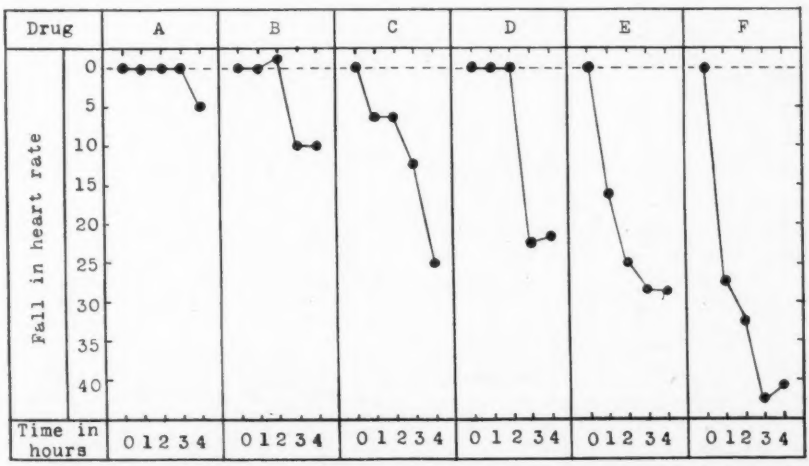

FIG. 20.—Rapid digitalization in a woman aged 36 with mitral stenosis and auricular fibrillation. (A) Strophanthin, 1/100 gr. intravenously. (B) Digoxin, 1·5 mg. by mouth. (C) Digoxin, 1·5 mg. chewed. (D) The same as C. (E) Digoxin, 1·5 mg. by mouth. (F) Digoxin, 1·0 mg. intravenously.

Ouabain was given intravenously in a dose of 1/240 gr. to two cases. It produced no effect in one case and only a slight effect in another. It was not given a sufficient number of times to justify any comparison with other drugs.

Strophosid

Strophosid (Sandoz) in a dose of 1 ml. containing 0·5 mg. of k-strophanthosid, was given 9 times. It produced a good effect in 5, a moderate effect in 2, and a slight effect in 1 case. In one there was a considerable fall during the first two hours, but the heart rate had returned almost to its previous level by the fourth hour. In the absence of any previous reports of the drug, the dosage of 1 ml. recommended by the manufacturers was regarded as a full dose. It was compared with strophanthin intravenously 3 times, with ouabain once, with digoxin by mouth 8 times, with digoxin intravenously 5 times, with digitaline (Nativelle) by mouth 4 times, with digitaline (Nativelle) intravenously 3 times, and with lanatoside C intravenously 7 times. The results are summarized in Table II.

Digitalis tincture and leaf

The tincture was given by mouth 3 times in a dose of 2 drachms. It had practically no effect in 2 cases, and only a slight effect in one within four hours. Digitalis leaf by mouth in a dose of 6 grains was given 3 times. In one case its administration was followed by a slight rise in heart rate, in one by a slight fall and in the third there was no change. As the full comparable dose of digitalis leaf lies between 15 and 25 grains these results could not be compared with other preparations.

Digalen, a water soluble preparation of total digitalis alkaloids, was given twice intravenously in a dose of 1 ml. It produced a good effect in one case, and a moderate effect in the other. It was not given a sufficient number of times to allow comparison with other drugs.

Digitaline (*Allen and Hanbury*) was given three times by mouth in a dose of 1/30 gr. (2·2 mg.). In no case did a significant fall in the heart rate occur within four hours.

TABLE II

THE EFFECT OF STROPHOSID INTRAVENOUSLY COMPARED WITH THAT OF OTHER PREPARATIONS

Drug for comparison	No. of trials	Efficiency of Strophosid intravenously compared with that of other preparations					
		Within 2 hours			Within 4 hours		
		Greater	Equal	Less	Greater	Equal	Less
Strophanthin	3	2	1	—	2	1	—
Ouabain	1	1	—	—	1	—	—
Digalen	2	1	—	1	1	—	1
Digitaline (Nativelle) (m) ..	4	2	2	—	1	—	3
Digitaline (Nativelle) (v) ..	3	—	—	3	—	—	3
Digoxin (m)	8	4	1	3	2	1	5
Digoxin (v)	5	3	—	2	3	—	2
Lanatoside C (v)	7	3	1	3	3	1	3

TABLE III

THE EFFECT OF DIGITALINE (NATIVELLE) BY MOUTH COMPARED WITH THAT OF OTHER PREPARATIONS

Drug for comparison	No. of trials	Efficiency of digitaline (Nativelle) by mouth compared with that of other preparations					
		Within 2 hours			Within 4 hours		
		Greater	Equal	Less	Greater	Equal	Less
Strophanthin	1	—	—	1	1	—	—
Strophosid	4	—	2	2	3	—	1
Digitaline (Nativelle) (v) ..	4	—	1	3	1	1	2
Digoxin (m)	5	3	1	1	1	—	4
Digoxin (v)	3	1	—	2	1	—	2
Lanatoside C (v)	5	—	1	4	—	1	4

TABLE IV

THE EFFECT OF DIGITALINE (NATIVELLE) INTRAVENOUSLY COMPARED WITH THAT OF OTHER PREPARATIONS

Drug for comparison	No. of trials	Efficiency of digitaline (Nativelle) intravenously compared with that of other preparations					
		Within 2 hours			Within 4 hours		
		Greater	Equal	Less	Greater	Equal	Less
Strophosid	3	3	—	—	3	—	—
Digitaline (Nativelle) (m) ..	4	3	1	0	2	1	1
Digoxin (m)	2	2	—	—	1	—	1
Digoxin (v)	6	2	—	4	2	—	4

Digitaline (Nativelle)

This preparation was given by mouth 8 times; once as 1·25 mg. with slight effect, once as 1·3 mg. with moderate effect, once as 1·5 mg. with good effect, once as 1·75 mg. with good effect, and four times as 2 mg.; with this dosage it had a good effect twice, moderate once, while on one occasion there was no fall in the heart rate. The full dose by mouth is generally accepted as 1·2 mg. and this was taken as the minimum for purposes of comparison. It was compared with strophanthin intravenously 4 times, with digoxin by mouth 5 times, with digoxin intravenously 3 times, and with lanatoside C intravenously 5 times (see Table III). It was given intramuscularly in a dose of 0·27 mg. in one case when a slight fall in heart rate occurred.

It was given 7 times intravenously. Once in a dose of 0·22 mg. it produced a sustained fall in heart rate; three times in a dose of 1·2 mg. it had a good effect and 3 times as 1·5 mg. it also had a good effect. The full intravenous dose is generally accepted as 1·2 mg. It was compared with strophosid intravenously three times, with digitaline (Nativelle) by mouth four times, with digoxin by mouth twice, and with lanatoside C intravenously six times. The results are shown in Table IV.

Digoxin

The relationship of the oral to the intravenous dose of digoxin, and the size of the full therapeutic dose was studied in 11 cases, because this did not appear to be known and because the full doses which have been generally recommended appeared to be inadequate. The effectiveness of digoxin when chewed was studied on three occasions. In one case, 1·5 mg. was chewed with the same effect on two occasions. The same dose was swallowed twice by this patient, producing once a slightly better effect than when it was chewed, and on the other a much lesser effect. In another case, 1·5 mg. was chewed on one occasion and swallowed on another. It produced a better effect when chewed, but the actual fall in heart rate was not great and the difference in effect of the two methods of administration was slight.

In two cases an equal dose was given intravenously and orally. In each a very much better effect was obtained with the intravenous dose. In one case an oral dose one-third times larger than the intravenous dose was given; the intravenous dose was slightly more effective. On seven occasions the oral dose was one-half times larger than the intravenous dose and each time the intravenous

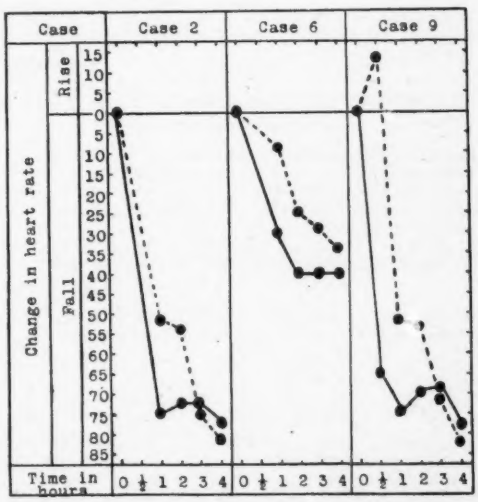

FIG. 21.—A comparison of the effects of digoxin given by mouth and half the amount given intravenously in three cases. In Case 2 digoxin, 3·0 mg. was given by mouth (represented by discontinuous lines) and 1·5 mg. intravenously (continuous lines). In Case 6 digoxin, 2·0 mg. was given by mouth and 1·0 mg. intravenously. In Case 9 digoxin, 3·0 mg. was given by mouth and 1·5 mg. intravenously.

dose produced a better effect, usually much better. In two cases the oral dose was twice the intravenous dose, and an equal effect was obtained. In a third case an oral dose twice the intravenous dose was given on two occasions; the intravenous dose was slightly more effective (Fig. 21). Although occasionally the effect of digoxin by mouth was not complete within four hours, any further effect was very slight.

Digoxin was given by mouth 18 times. It was given as 1·0 mg. once with good effect, as 1·25 mg. once with moderate effect, as 1·5 mg. eight times, as 2·0 mg. four times, and as 3·0 mg. four times. In the 8 cases that received 1·5 mg. a good effect was seen three times, a moderate effect four times, and no effect once. With a dose of 2·0 mg. a good effect was seen three times, and there was no fall in the heart rate in one case. With a dose of 3·0 mg. a good effect was seen in all four cases. The minimal full dose was regarded as 1·25 mg. for the purpose of comparison. It was compared with strophanthin intravenously 14 times, with ouabain intravenously twice, with strophosid intravenously 8 times, with digalen intravenously twice, with digitaline (Nativelle) by mouth 5 times, with digitaline (Nativelle) intravenously twice, with digoxin intravenously 14 times, and with lanatoside C intravenously 7 times. The results are shown in Table V.

Digoxin was given intravenously 14 times. It was given as 1·0 mg. 8 times, producing a good effect in seven and a moderate effect in one, as 1·25 mg. twice, producing a good effect once, and an ectopic rhythm in the other, as 1·5 mg. 4 times producing a good effect 3 times and a moderate effect once. The minimum full dose intravenously was regarded as 1·0 mg. It was compared with strophanthin intravenously ten times, with ouabain intravenously twice, with strophosid intravenously five times, with digalen twice, with digitaline (Nativelle) by mouth three times, with digitaline (Nativelle) intravenously four times, with digoxin by mouth fourteen times, and with lanatoside C intravenously eight times. The results are shown in Table VI.

TABLE V

THE EFFECT OF DIGOXIN BY MOUTH COMPARED WITH THAT OF OTHER PREPARATIONS

Drug for comparison	No. of trials	Efficiency of digoxin by mouth compared with that of other preparations					
		Within 2 hours			Within 4 hours		
		Greater	Equal	Less	Greater	Equal	Less
Strophanthin	14	7	1	6	12	—	2
Ouabain	2	1	1	—	2	—	—
Strophosid	8	3	1	4	5	1	2
Digalen	2	1	1	—	1	—	1
Digoxin (v)	14	—	—	14	3	3	8
Digitaline (Nativelle) (m) ..	5	1	1	3	4	—	1
Digitaline (Nativelle) (v) ..	2	—	—	2	1	—	1
Lanatoside C (v)	7	3	—	4	4	—	3

TABLE VI

THE EFFECT OF DIGOXIN INTRAVENOUSLY COMPARED WITH THAT OF OTHER PREPARATIONS

Drug for comparison	No. of trials	Efficiency of digoxin intravenously compared with that of other preparations					
		Within 2 hours			Within 4 hours		
		Greater	Equal	Less	Greater	Equal	Less
Strophanthin	10	8	1	1	9	1	—
Ouabain	2	2	—	—	2	—	—
Strophosid	5	2	—	3	2	—	3
Digalen	2	2	—	—	1	1	—
Digitaline (Nativelle) (m) ..	3	2	—	1	2	—	1
Digitaline (Nativelle) (v) ..	4	2	—	2	2	1	1
Digoxin (m)	14	14	—	—	8	3	3
Lanatoside C (v)	8	2	1	5	2	—	6

Lanatoside C

Lanatoside C was given by mouth 5 times. Once in a dose of 1·0 mg. there was a temporary fall in the heart rate, which, however, rose almost to its previous level within four hours. It was given four times as 3·0 mg. In one case a fall in heart rate did not occur, in another there was a slight fall, while in a third a moderate fall took place. In the last three there was an initial fall in rate, but it returned to the previous level within three hours. As the full dose of lanatoside C is probably about 10 mg. by mouth, for its rate of absorption is variable, its effect could not be compared with that of other preparations.

Lanatoside C was given intravenously 11 times. In a dose of 0·8 mg. it had a good effect in two cases, and moderate in one. As 1·0 mg. it was given once producing a moderate effect, and as 1·2 mg. once producing a good effect. It was given 6 times as 1·5 mg. with a good effect in all cases. For purposes of comparison 0·8 mg. intravenously was regarded as a full dose. It was compared with strophanthin intravenously three times, with ouabain intravenously once, with strophosid intravenously seven times, with digalen intravenously twice, with digitaline (Nativelle) intravenously six times, with digitaline (Nativelle) by mouth five times, with digoxin by mouth seven times, and with digoxin intravenously eight times. The results are shown in Table VII.

nine, and digitaline (Nativelle) intravenously once out of six. Intravenous digoxin was given 14 times and a very rapid effect was seen 8 times. With lanatoside C intravenously a very rapid effect occurred in 7 out of 10 trials.

Toxic effects. Several cases experienced slight nausea after some preparations, but in only three cases did vomiting occur. Paroxysmal tachycardia occurred in one patient 1½ hours after receiving 1·25 mg. of digoxin intravenously ; it lasted for 10 hours and was not accompanied by any distress.

Discussion

In earlier times ideas on the *dosage* of digitalis became confused, and its value to some extent suffered on this account. Generally it was used in inadequate doses, and in the absence of any method of standardizing the strength of such a potent drug it is not surprising that physicians tended to err on the side of under-dosage. Many workers have pointed out the variations in potency of preparations assayed by animal experiments and the differences in effect, when applied to man, of preparations having the same potency by animal assay (Cushny, 1925 ; Gold *et al.*, 1941 *a*, *b* ; Gold and Cattell, 1941 ; Lyon and Gilchrist, 1927), but the introduction of such pharmacological assay has nevertheless been a great advance in the use of digitalis.

Mackenzie (1914) advised "steadily to push the

TABLE VII

The Effect of Lanatoside C Intravenously Compared with that of Other Preparations

Drug for comparison	No. of trials	Efficiency of lanatoside C intravenously compared with that of other preparations					
		Within 2 hours			Within 4 hours		
		Greater	Equal	Less	Greater	Equal	Less
Strophanthin	3	2	1	—	2	—	1
Ouabain	1	1	—	—	1	—	—
Strophosid	7	3	1	3	3	1	3
Digalen	2	1	—	1	1	—	1
Digitaline (Nativelle) (m) ..	5	4	1	—	4	1	—
Digitaline (Nativelle) (v) ..	6	4	—	2	4	—	2
Digoxin (m)	7	4	—	3	4	—	3
Digoxin (v)	8	5	1	2	6	—	2

Very rapid digitalis action. Full digitalis effects within one hour were only seen with intravenous administration. A fall occasionally occurred within 15 to 30 minutes. Strophanthin produced such a rapid effect once in a dose of 1/60 gr., out of a total of nine intravenous administrations. Strophosid produced a very rapid effect three times out of drug, whichever preparation is employed, until a reaction is observed." He then omitted the drug for a few days, starting again on half the dosage until further adjustment became necessary. He advocated instructing the patient in the symptoms of overdosage, and found that most patients by their own sensations quickly acquired the knowledge of how

much of the drug was needed. Mackenzie recorded an interesting example of the intelligent use of the drug by a patient who came under his care and who made his own infusion of foxglove and was in the habit of taking the drug whenever he was unable to lace up his boots. He mainly employed the tincture, giving one drachm daily, in doses of 15 to 20 minims, in cases of marked failure until a reaction was observed, but in cases of great distress and urgency he used 2 drachms daily when the effect was usually seen in two to three days. He stressed that its dosage must be determined individually for each patient.

Cushny (1925) wrote that the best results are obtained only by the largest doses which can be given without gastric or intestinal symptoms, and this principle with certain modifications has been reiterated by nearly all writers on the subject since. A study of methods of rapid digitalization began with Eggleston's (1915) work on the dosage of digitalis. He found that the average dose of the tincture necessary to produce an ideal therapeutic effect was 0·146 cat units per lb. weight, i.e. about 22 cat units for a patient of 150 lb. ; this is roughly equivalent to 33 grains of digitalis leaf. White and Morris (1918) tried the method and reported favourably on it. Fraser (1922) employed it in 14 cases using slightly smaller doses and concluded that it was very useful in suitable cases. The amount calculated by Eggleston was that necessary to produce a full therapeutic effect just short of toxic doses, and in fact in many cases it did produce toxic effects. That this dose is greater than that necessary to produce a therapeutic effect has been pointed out by many workers. Marvin (1928) stated that his custom in rapid digitalization was to calculate the amount according to Eggleston's formula, and then to give a little less than the total amount. Robinson, White, Eggleston, and Hatcher (1924) and Levy and Mackie (1927) found that 22 grains (1·5 g.) of digitalis leaf was the average dose necessary to produce full therapeutic effect within forty-eight hours in an adult. It came to be accepted that the dose of digitalis that would produce the optimum effect was less than that necessary to produce any toxic effect in the great majority of cases, that there was in fact a wider therapeutic range to the drug, and that "full dose" digitalization in accordance with Eggleston's original studies was undesirable. Luten (1937) felt that the ideal plan was to ascertain the optimum level of dosage for each individual patient.

The divided dose method of Eggleston, used by the above workers, allows of alteration in the succeeding doses, if indicated by the patient's irregular response to the drug, although the total amount likely to be required was calculated in advance. Attempts to give the whole dose at once have been looked on with disfavour for many reasons. Individual susceptibility to digitalis has sometimes resulted in toxic reaction to an average dose. The inconstant response to doses calculated in accordance with the body weight has been pointed out by Lyon and Gilchrist (1927), while Gold and Travell (1941) found that the body weight was only one factor determining the amount of digitalis necessary for individual patients. The relative inconstancy of preparations assayed by biological methods was a further drawback to their use for massive-dose digitalization. A method of assaying digitalis in man has been produced to overcome the variable effects from preparations assayed in cats (Gold *et al.*, 1942), but it is unlikely to be generally applied. This difficulty, however, is removed by the use of the purified glucosides, in which the dosage by weight has been determined directly in man. Further, the liability of large doses of digitalis tincture and leaf to produce vomiting from its local effect, apart from the central vomiting occurring later when the patient is saturated with the drug, does not apply to the same extent in the case of certain purified glucosides. The absorption of digitalis, although apparently only about 20 per cent, is fairly constant (Eggleston and Wyckoff, 1922 ; Wyckoff and Goldring, 1927), and this favours its use in large doses. The most important objection to the production of full digitalis effects by one dose would appear to lie in the individual variability of the amount required, but since there is a therapeutic range of digitalis dosage, within which the optimum lies, it is unnecessary to give doses just short of producing toxic effects. Gold and De Graff (1930) emphasized the wide margin of safety between the minimal therapeutic and the toxic doses. They also said that in the average ambulatory cases with auricular fibrillation and some heart failure, much less digitalis was required to produce a full effect than was necessary with more severe heart failure, and that in the former cases there was a wide margin of safety between therapeutic and toxic doses; this margin, however, diminished as the failure became more severe. They also pointed out that the effective concentration within the body necessary to maintain full effects was less than that required to initiate them.

In spite of the opinions against one-dose methods, the experience of many workers indicates that under certain conditions the method is safe and in our view it is desirable. Robinson (1920) tried the effect of a single large dose of digitalis, and gave 15 to 25 ml. of the tincture of digitalis to 26 patients without producing toxic effects; he concluded that the method was safe under controlled conditions. In

a series of studies of digitalis medication, Gold and his co-workers (1942 and 1944) have had a wide experience of single dose method of digitalization in which digitalis sufficient to saturate the patient is administered. Digitaline, in view of its constant potency and the fact that in their opinion it is almost completely absorbed, was mostly used and in 1944 they summarized their results, having given this preparation to more than a thousand patients. They found that 1·20 or 1·25 mg. (equivalent to 3 cat units) by mouth, produced full digitalization in the average patient, and that minor toxic symptoms such as nausea and vomiting occurred in less than 5 per cent; the effect was complete in four to ten hours. When using an amount of digitalis leaf necessary to produce an equivalent result, which they found to be from 12 to 20 cat units, vomiting occurred in 20 per cent of cases. They stated that digitaline by this method was safe and effective. Maintenance dosage could be started on the following day and adjusted as necessary, or in cases where a full effect had not been produced within twenty-four hours, a larger dose than would normally be required for maintenance could be given on the second day. Katz and Wise (1945) confirmed the safety and efficiency of Gold's method, but stated that they preferred the divided dose technique.

The water-soluble preparations of digitalis leaf for *intravenous use* vary in their potency and this has lessened their value (Haag and Hatcher, 1929 ; Levy, Bruenn, and Ellis, 1932). Strophanthin intravenously, introduced by Fraenkel and Schwarz (1907), became popular and has remained so on the continent and in Latin America until the present time. Indeed, the question of the value of intravenous therapy in the past has been partly concerned with the relative value of strophanthin as a cardiac remedy. Owing to the development of the Eggleston method of rapid digitalization in this country and America, intravenous digitalis therapy was not common practice until the purified digitalis glucosides came into use in recent years. Mackenzie (1914) stated that intravenous strophanthin may be given in doses of 1/250 gr., but considered that it was needed only in exceptional and urgent cases, for he had rarely failed to get a reaction in good time by giving digitalis by mouth. The main advantage of intravenous digitalis therapy lies with its rapidity of action. A digitalis effect may be seen within a few minutes. The presence of gastro-intestinal upset is a further indication for its use (Wenckebach, 1910), and rectal administration is a poor alternative.

Precision in dosage has been advanced as an argument in its favour (Fraenkel, 1935), because the uncertainty of intestinal absorption is eliminated. The dangers attendant on intravenous therapy have been pointed out by many authors. Robinson *et al.* (1924) stated that intravenous digitalization should only be used after an adequate appreciation of these and especially where digitalis seems to be urgently required. Clarke (1924) spoke against its intravenous use. Luten (1937) expressed no enthusiasm for intravenous therapy, but stated that when the method had to be employed, the slow injection of ouabain, well diluted and in conservative amount, probably afforded the least objectionable procedure. Fishberg (1940) stated that the hope of attaining success by the intravenous administration of digitalis to patients in whom large doses of the drug by mouth failed to produce improvement had always proved illusory in his experience. The intravenous use of strophanthin or digitalis, since the introduction of the purified glucosides, has more recently been advised in urgent cases by many authorities including Lewis (1937), Parkinson (1940), and White (1944).

Methods of assay, chemical analysis, and the isolation of pure glucosides have rendered digitalis therapy simpler and safer, but the exact amount required in an individual case has still to be determined by trial and error in a manner similar to that employed by Withering. Its effect in reducing the heart rate in auricular fibrillation, long known to parallel closely its beneficial effects and to be responsible for many of them, provides a method for the measurement of clinical benefit—not perfect, but the best available. Gavey and Parkinson (1939) discussing the effects of digitalis on patients with auricular fibrillation said that most of those with slowing of the heart rate also showed clinical benefit, but in the absence of slowing there was no benefit. When the effect of *oral* and intravenous administration of the digitalis preparations was compared (Table VIII) preparations given intravenously gave more consistent results within four hours than when given orally. The difference, although significant, was not great, and was partly due to the fact that some of the oral doses were too small for particular patients. The impossibility of forecasting the correct dosage in advance is the chief difficulty in reaching a satisfactory comparison of the oral and intravenous methods of administration.

Strophanthin in a dose of 1/100 gr. gave inconstant and poor results. In a dose of 1/60 gr. it produced a good effect in three out of four cases, but this is much larger than the maximum safe dose in the view of most writers. Strophosid gave better results than strophanthin; it produced a good effect in five out of nine cases, a rapid action being seen in three cases. It worked better than strophanthin twice, and as well once, in the three cases in which

TABLE VIII

THE EFFECTIVENESS OF DIGITALIS PREPARATIONS IN DIFFERENT DOSAGE, AND GIVEN BY MOUTH OR INTRAVENOUSLY

Preparation	Dosage	No. of trials	Therapeutic effect			
			Good	Moderate	Slight	None
Strophanthin (v)	1/100 gr.	6	1	—	1	4
	1/60 gr.	4	3	—	1	—
Strophosid	1 ml.	9	5	2	2	—
Digitaline (Nativelle) (m) ..	1·25 mg.	1	—	—	1	—
	1·30 mg.	1	—	1	—	—
	1·50 mg.	1	1	—	—	—
	1·75 mg.	1	1	—	—	—
	2·00 mg.	4	2	1	—	1
Digitaline (Nativelle) (v) ..	1·20 mg.	3	3	—	—	—
	1·50 mg.	3	3	—	—	—
Digoxin (m)	1·00 mg.	1	1	—	—	—
	1·25 mg.	1	—	1	—	—
	1·50 mg.	8	3	4	—	1
	2·00 mg.	4	3	—	—	1
	3·00 mg.	4	4	—	—	—
Digoxin (v)	1·00 mg.	8	7	1	—	—
	1·25 mg.	2	1	—	—	1*
	1·50 mg.	4	3	1	—	—
Lanatoside C (v)	0·80 mg.	3	2	1	—	—
	1·00 mg.	1	—	1	—	—
	1·20 mg.	1	1	—	—	—
	1·50 mg.	6	6	—	—	—

* Toxic effect.

the drugs were compared. Yet, it did not produce the consistent results obtained from digitalis preparations, and we have found no justification for the continued use of strophanthin or strophosid.

Digitaline (*Nativelle*) by mouth was somewhat inconstant in its action in the dosage tried. It seemed that the doses used by us were too small, and this is in accordance with the view of Stewart (1945) who regarded 2·0 mg. as an average dose. In the few cases in which the effect of the intravenous and oral administration of the drug was compared, no support could be found for the contention that it is completely absorbed (Gold *et al.* 1941 and 1942). Intravenously, however, it produced consistently good effects within two hours in a dose of 1·2 or 1·5 mg., and compared satisfactorily with both digoxin and lanatoside C. A more rapid effect, namely, within the first hour, was only seen once in six cases, and therefore less often than with the other two preparations.

Digoxin by mouth did not produce consistent results in a dose less than 2·0 mg. A good effect was seen in all four cases who received 3·0 mg., and no toxic effect was seen with this dose. It would appear that a dose of at least 2·0 mg. by mouth is advisable if a full digitalis effect is required within four hours. A much more rapid effect was seen when the drug was given intravenously. In the fourteen cases in which the two methods of administration were compared, a better effect was seen in all during the second hour with intravenous administration. Intravenously, digoxin produced a good effect in the great majority of cases and a very rapid effect was seen in more than half. When compared with intravenous lanatoside C, however, it was not so effective in six out of eight cases. *Lanatoside* C intravenously in a dose of 1·5 mg. produced a good effect in all of six cases to which it was given. Of the ten cases who received this drug a very rapid effect was seen in seven. Thus, it gave better results than any other preparations when used intravenously, but only slightly better than digoxin.

Where a digitalis effect is required within an hour intravenous administration is the method of choice, and the attendant risks of such therapy are small. These investigations showed that lanatoside C and

digoxin were the best preparations for intravenous use; the slightly better results obtained with lanatoside C are within the limits of experimental error. With oral administration the results obtained with different dosage have naturally varied, but a full effect within four hours can be ensured if an appropriate dose of digoxin is used.

Conclusions

Strophanthin and a number of digitalis preparations were submitted to a clinical trial in 20 patients with auricular fibrillation and heart failure with the object of discovering the best means of bringing about a digitalis effect quickly (rapid digitalization).

Digoxin and lanatoside C proved to be the best and digitaline (Nativelle) was scarcely less efficient.

Should it be necessary to induce digitalization within two hours, digoxin as 1·5 mg. intravenously or as 2·0 to 3·0 mg. orally, and lanatoside C as 1·5 mg. intravenously only, can best accomplish it.

To establish adequate digitalization within four hours digoxin as 2·0 mg. by mouth is an effective method.

As it is seldom necessary to obtain a digitalis effect in less than two to three hours, and as intravenous medication may be less convenient, digoxin as 2·0 to 3·0 mg. by mouth is generally the best way to induce rapid digitalization.

We wish to thank Dr. Donald Hunter and Dr. A. E. Clark-Kennedy for allowing us to treat four patients under their care. Sir John Parkinson, Physician to the Cardiac Department, has given us advice on the preparation of this paper.

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THE RELATIVE VALUE OF DIGITALINE PREPARATIONS IN HEART FAILURE WITH AURICULAR FIBRILLATION

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At the present time there are at least six digitaline preparations in use in this country. Digitaline, first isolated by Nativelle (1869), consists of digitoxin with traces of other glucosides and impurities. In the *British Pharmaceutical Codex* (1934) the only standards stipulated for the drug are a melting point not below 240° C., and a loss of not more than 1 per cent at 100° C. Although the drug is not a pure substance there is no obligation for a manufacturer to carry out a biological assay of the preparation, and it may be dispensed by weight. Methods of manufacture vary slightly from one firm to another and the exact processes remain a secret in some instances. The use of digitaline has been recently advocated by Gold and his associates (Gold *et al.*, 1942; Gold *et al.*, 1944) on the grounds of its ready and almost complete absorption from the intestinal tract (Eggleston and Wyckoff, 1922; Gold and Travell, 1941). For this reason they regard it as particularly appropriate for rapid digitalization by a single adequate dose given by mouth. For maintained digitalization it is a satisfactory preparation, but there are good grounds for preferring digitalis leaf for routine use (Evans, 1940). Gold, Kwit, and Cattell (1940) found that 3 cat units of Nativelle's digitaline by mouth was equivalent to 25 cat units of digitalis leaf. As Cushny (1925) pointed out, the cat method is only useful to compare different samples of the same drug and to estimate their probable effect in man, and is of little value for the comparison of different preparations of digitalis given in treatment. Gold *et al.* (1940) found that Nativelle's digitaline by weight was two hundred times more potent than digitalis leaf standardized by the cat and frog methods, but was one thousand eight hundred times more potent in man when given by mouth. This difference is largely explained by the better absorption of digitaline. Evans (1940) found that 1/600 grain (0·25 mg.) of Nativelle's digitaline was equivalent to 1 grain of the powdered digitalis leaf, a finding in agreement with the observations of Campbell (1938). Digitaline (Allen and Hanbury), however, supplied in granules similar in appearance and dosage to Nativelle's digitaline, was not found to be so effective in a dosage of 1/240 grain, as was Nativelle's preparation in a dose of 1/600 grain (Evans, 1940).

The present work was undertaken to ascertain whether there was any variation in the value of six commercial preparations of digitaline when dispensed to patients with heart failure and auricular fibrillation. The method for this clinical assay was the same as that described by Evans (1940). The preparations tested, marketed by six different firms, were designated A, B, C, D, E, and F.

Thirteen patients, all of whom had been under observation for some time, were chosen for the clinical trial. Three failed to complete the course, two owing to irregular attendance and the third owing to admission to hospital with an exacerbation of heart failure, leaving 10 in the series; six were men and four women. Their ages varied from 24 to 63. Auricular fibrillation and heart failure were present in all, associated with hypertension in two and with mitral stenosis in the remaining eight. They were all treated as out-patients and they led their usual lives, the majority being at work. With one exception they had been receiving powdered digitalis leaf for prolonged periods before the tests. The patients attended each fortnight; their statement on progress was recorded at each visit, and after a short rest the apical rate was counted over three successive half-minute periods, and the average rate was taken. They were examined clinically and by cardioscopy at intervals according to need. At each attendance they were given a different digitaline preparation for the following test period of 14 days, thus ensuring that by the end of the period each patient had been fully under the influence of the fresh preparation for

a few days at least. One grain of powdered digitalis leaf and one pill (1/600 grain) of each digitaline preparation were given as single doses, while the number of doses a day was different for different patients according to their habitual requirements before the clinical trials were started, and it was kept constant for each patient throughout the investigation. The order in which the preparations were given was deliberately varied in each case. The following is an account of one case.

Male, aged 45, with mitral stenosis, aortic incompetence, auricular fibrillation, and heart failure

At the age of 11 the patient had rheumatic fever. He was prevented from playing games at school as a consequence of this, and was rejected from the army during the 1914–18 war on account of his heart. Twenty years ago he had a small hæmoptysis and a larger one thirteen years later. Dyspnœa had been present for seven years and recently this had become worse and was present at rest. In the last five weeks he had been unable to work. Hæmoptysis recurred a week before. He had been receiving digitalis for the last three months from his doctor who sent him to the Cardiac Department for treatment.

He was breathless when examined and showed slight cyanosis and venous congestion in the neck. The pulse was 80 and was irregular from auricular fibrillation. The blood pressure was 160/55. There was no œdema. The apex beat was displaced outwards to the anterior axillary line. Systolic and mid-diastolic murmurs were heard in the mitral area, as well as aortic, systolic, and diastolic murmurs. Fine crepitations were found at both bases and the liver was distended and tender. The urine was normal. Cardioscopy showed great cardiac enlargement, involving the left ventricle, left auricle, right auricle and the conus and pulmonary artery; there was moderate pulmonary congestion. He was admitted to hospital the same day and responded readily to treatment with rest, restricted fluids, digitalis and two injections of neptal. He was discharged four weeks later, with only slight pulmonary congestion, and he continued to take 1 grain of digitalis leaf twice daily. He was included in the present series on August 13, 1946, and his progress during the clinical trials is set out below in tabulated form.

Date	Medicine during previous 14 days	Digitalis dose (given twice daily)	Heart rate a minute	Patient's statement on progress
13 Aug.	Digitalis leaf	1 grain	68	Well
27 Aug.	Drug E	1/600 „	78	Well
10 Sep.	Drug C	1/600 „	65	Very well
24 Sep.	Drug A	1/600 „	81	Well
8 Oct.	Drug D	1/600 „	57	Very Well
22 Oct.	Drug F	1/600 „	87	Well
5 Nov.	Drug B	1/600 „	65	Well

Clinical signs of heart failure did not increase during the period of trials, and the urinary output was satisfactory.

The results for all six digitaline preparations are summarized in Table I.

TABLE I

HEART RATE IN TEN PATIENTS WITH AURICULAR FIBRILLATION AFTER TREATMENT WITH SIX DIFFERENT KINDS OF DIGITALINE

Case No.	Age	Sex	Weight in lb.	No. of doses daily	Drug A	Drug B	Drug C	Drug D	Drug E	Drug F	Average
1	24	F	149	3	109	85	87	85	91	87	91
2	58	M	180	2	83	68	85	73	76	63	75
3	44	M	144	2	103	82	85	84	79	77	85
4	47	M	132	2	82	70	73	79	82	89	79
5	59	M	127	2	97	81	73	99	82	108	90
6	48	M	146	2	109	95	102	80	81	101	95
7	63	M	201	2	114	104	79	84	80	113	96
8	45	M	126	2	81	65	65	57	78	87	72
9	27	F	101	2	53	65	61	51	58	52	57
10	56	M	140	2	87	79	77	79	87	81	82
		Average			92	79	79	77	79	86	

The results were examined statistically by the analysis of variance method (Fisher, 1937). There was found to be a significant difference between the effect of the drugs, due to the high heart rates obtained with drug A, and the probability of this difference occurring by chance was less than 1 in 100.

In order to check these findings another series of trials was carried out with the same digitaline preparations on twelve other patients with auricular fibrillation and heart failure. Three patients had to be excluded from the series owing to irregular attendance, and two on account of an increase in the severity of the heart failure necessitating admission to hospital. In the seven remaining patients mitral stenosis was the underlying cause of the heart failure in four and hypertension in three. The same procedure was followed in carrying out the trials but the order in which the drugs were given was decided by drawing lots. The results are summarized in Table II.

Applying the same statistical method to the results in Table II, Drug A is again found to be significantly inferior to the remaining five preparations, the probability of such a result arising by chance being about 1 in 21.

It is apparent from these two series of trials that

TABLE II

HEART RATE IN SEVEN PATIENTS WITH AURICULAR FIBRILLATION AFTER TREATMENT WITH SIX DIFFERENT KINDS OF DIGITALINE AND WITH POWDERED DIGITALIS LEAF

Case No.	Age	Sex	Weight in lb.	No. of doses daily	Drug A	Drug B	Drug C	Drug D	Drug E	Drug F	Digitalis leaf	Average
1	64	M	201	2	101	70	85	77	91	83	81	84
2	54	M	126	2	102	97	87	90	87	90	89	92
3	67	F	115	2	91	89	97	101	80	91	81	90
4	42	F	154	2	85	82	86	39	87	91	67	82
5	36	M	143	2	113	69	73	81	77	72	70	79
6	45	M	126	1	74	60	66	71	69	65	71	68
7	54	F	132	1	79	81	70	83	83	87	89	81
Average					92	78	81	83	82	83	78	
Average for first series					92	79	79	77	79	86		

Drug A is not as efficacious as the remaining preparations. There was no significant difference between the effects of the other drugs. It is now recognized that the dosage of digitalis necessary to produce an adequate clinical effect in any given patient lies within a fairly wide range, particularly when there is only slight or moderate heart failure present (Gold and De Graff, 1930), and it is probable that the inferiority of Drug A demonstrated in these two series of trials represents a fairly considerable difference of potency. It is unsatisfactory that preparations with the same or similar names, but differing in clinical potency, should be marketed by different firms. A practitioner prescribing digitaline cannot be certain that his patient will always receive a preparation of the same potency, and undesirable toxic effects may be produced by one drug, while another may have an inadequate effect. There is no obligation on the manufacturers to standardize their products by biological assay, nor is it certain to what extent this would result in a greater uniformity of digitaline preparations. The explanation of the inconsistent results obtained with digitaline preparations may lie in the method of manufacture. In some instances certain stages of the procedure are a closely guarded commercial secret, and there is no certainty that the final products are identical with the different processes used, thus rendering the standardization of different digitaline preparations by biological assay of less value. Digitalis leaf has been found to produce consistent clinical results by many observers. Its method of preparation is known to all and is simple, and its standardization by biological assay is adequate for clinical purposes. It is suggested that if a standard method of preparation were laid down for digitaline, as it is for digitalis leaf, and biological assay of the product were compulsory, variations in potency might be reduced. At the present time powdered digitalis leaf would appear to be preferable for maintained digitalization.

SUMMARY

The effect of six different commercial preparations of digitaline has been tried in two series of ten and seven patients with heart failure and auricular fibrillation. One preparation was much less effective than the other five in both trials. It is suggested that a standardized procedure for the manufacture of digitaline should be introduced, and that biological assay should be made compulsory. The variability in the potency of digitaline preparations suggests the advisability of using digitalis leaf for continuous digitalization at the present time.

I wish to thank Dr. D. Jennings for his advice on the statistical analysis of the results of this investigation.

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THE HEART IN RHEUMATOID ARTHRITIS

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Recent reports suggesting the presence of cardiac lesions at autopsy in a high proportion of patients with rheumatoid arthritis appear to be in conflict with clinical experience. In view of the scarcity of comprehensive clinical, and the absence of radiological studies of the heart in rheumatoid arthritis, and also of the contradiction between clinical and pathological findings, there appears to be a need of further clinical and radiological material.

The incidence of heart disease at autopsy in patients suffering from what is variously called nodular rheumatism, chronic rheumatism, and genuine arthritis deformans is, in earlier studies, given as between 30 to 50 per cent (Charcot, 1881; Kast, 1901; Grzimek, 1932; Klinge, 1933), the heart disease being more frequent in secondary than in primary chronic rheumatism. Changing conceptions of the ætiology and classification of rheumatic diseases in more recent years are an obstacle to the direct evaluation of these findings.

More recently cardiac lesions " indistinguishable from those of rheumatic fever " were described in 56 per cent of 24 patients with rheumatoid arthritis at necropsy by Baggenstoss and Rosenberg (1941 *a*, *b*), in 22 per cent of 23 patients by Bayles (1943), and in 66 per cent of 38 patients by Young and Schwedel (1944).

In a clinical study Dawson (1933) found 7 cases of manifest rheumatic heart disease in 100 patients suffering from rheumatoid arthritis. Colver (1937) in 69 children with Still's disease detected carditis during life in only 1; of 4 studied at autopsy none had carditis. Hench and Rosenberg making a study of all their arthritic patients on a given date (1941) found none with clinical or electrocardiographic evidence of carditis. The incidence of clinically manifest rheumatic heart disease in a series of rheumatoid arthritis patients, examined by Bayles and McGinn (1943) was 5 per cent. Young and Schwedel's series (1944) occupies a unique place here, since the diagnosis of rheumatic heart disease was made during life in 18 of 32 patients with rheumatoid arthritis: this, together with the high number of positive cardiographic findings, suggests selective accumulation of patients with heart disease. Elman (1944) in 100 patients with rheumatoid arthritis found 8 with " rheumatic carditis," 5 of whom gave no history of rheumatic fever; he also observed 22 patients in whom rheumatic carditis coexisted with rheumatoid arthritis. Rogen (1947) found only one patient with mitral disease in a group of 33 with rheumatoid arthritis.

Material and Methods

The 60 patients studied here were selected from 150 patients with rheumatoid arthritis, after eliminating those where the clinical picture was not typical, where rheumatic fever occurred in the past, where chest deformity or inability to stand upright prevented satisfactory radioscopy, and where records were not sufficiently complete. The criteria of diagnosis were those laid down by the Committee of the International League against Rheumatism (1934), Poynton and Schlesinger (1937), and a Committee of the American Rheumatism Association (1942). The clinical picture was regarded as typical if the smaller joints of the hand were characteristically involved in addition to the larger joints, and if joint involvement was accompanied by all or most of the following signs of general systemic involvement: anæmia, weight loss, general malaise, easy fatigability, and increased sedimentation rate. Patients in whom the process was limited to the larger joints or to a single joint, those in whom its onset coincided with the menopause, and those with a history of rheumatic fever or with

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raised blood pressure were excluded. Selection in this manner resulted in a group of patients with normal blood pressure, suffering from advanced rheumatoid arthritis of considerable duration.

Forty-three of the 60 patients were women. Ages ranged from 25 to 69 years, 5 being in the third, 6 in the fourth, 13 in the fifth, 21 in the sixth, and 15 in the seventh decade. Healed pulmonary tuberculosis was found in 2 patients (Cases 4 and 32), and duodenal ulcer in 1 (Case 49). From each patient a relevant history was taken and a careful physical examination made, including X-ray and electrocardiogram.

Clinical Manifestations of Heart Disease

Only 3 of these 60 patients presented clinical manifestations of heart disease.

Case 9, male, aged 59, with extensive articular involvement, was the only one in the series who had a mitral diastolic murmur. Radiologically his heart showed moderate left ventricular enlargement. Displacement of the barium filled gullet as a result of left auricular enlargement was not present and the electrocardiographic record was normal. Subjective symptoms related to the heart were absent.

Two patients, both women, aged 69 and 62 respectively (Cases 2 and 30), displayed signs of heart failure with congestion. There were no acoustic abnormalities, the cardiac silhouette was normal, and satisfactory response to digitalis and mercurial diuretics was obtained in both. The electrocardiogram in Case 2 showed auricular fibrillation. In the absence of signs of valvular involvement and in view of the patient's age, heart failure due to coronary disease appears the leading possibility with rheumatic heart disease not excluded.

Faint systolic apical murmurs were found in a number of patients. Some complained of slight shortness of breath and palpitation. Apart from the patients with frank heart failure these symptoms were mild, and it seems that their presence is of no specific significance in view of the anæmia and general debility characteristic of rheumatoid arthritis.

Electrocardiographic Changes in Rheumatoid Arthritis

Master and Jaffee (1932) taking daily cardiograms in 17 patients for 53 days, found only the slightest evidence of myocardial involvement. Logue and Hanson (1944) in 100 cases with prolonged P–R interval found that rheumatoid arthritis has been present in 5. Young and Schwedel (1944) found changes in 7 of 22 patients, 4 having auricular fibrillation. The changes in rheumatic carditis are transient and very variable, most cardiographic abnormalities having been encountered and a prolonged P–R interval being the most frequent.

We have examined 131 cardiograms in these 60 patients, and except for low voltage curves have found only 3 with significant changes. A woman, aged 46, with typical active rheumatoid arthritis had a normal curve, but a year later, when she was improving after chrysotherapy, had S–T depression in the first and elevation in the third lead. A man, aged 69, had a normal curve first, but later developed auricular fibrillation and congestive heart failure. A male, aged 69, with some cardiac enlargement, had a P–Q interval of 0·22 seconds. As the second and third patients were 69, these findings have little, if any, significance.

Low Voltage. Low voltage in the standard leads has occurred more frequently in the present series than any other single cardiographic abnormality. A voltage of all deflections in all leads of 0·5 mV or less is regarded as abnormal, and was found in 5 of the 60 patients (8 per cent). Low voltage has been associated with other cardiographic abnormalities in 2 patients, and with radiological cardiac enlargement and congestive heart failure in one of these. The 3 other patients of this group have presented no further evidence of heart disease. The ages of the 5 patients with low voltage were 57, 67, 67, 69, and 69 years. In 18 patients (30 per cent) the voltage was 0·8 mV or less.

The incidence of low voltage in healthy subjects shows considerable variation from author to author. It ranges from none (Shipley and Hallaran, 1936; Hoskin and Jonescu, 1940; and Larsen and Skulason, 1941), 1·8 (Viscidi and Geiger, 1943), and 3 per cent (Levitt, 1939; Chamberlain and Hay, 1939) to 6 per cent (Leach, Reid, and White, 1941), and 8 per cent (McFarland *et al.*, 1939). A voltage of less than 0·8 mV was found in 30 per cent by McFarland *et al.* (1939). That age does not determine the occurrence of low voltage is suggested by the fact that both the Viscidi and Geiger (1943) and the McFarland (1939) groups consisted of young, healthy airmen.

In order to obtain further information, minimum, maximum, and average values of R I, R II, and R III in the first tracing obtained from each patient were determined. Table I shows a comparison between values found in this series and normal controls reported by other workers in healthy subjects and also a control series of 50 healthy subjects.

In the present series the incidence of voltage below 0·5 and below 0·8 mV respectively is as high as the highest in published work. It is higher than in a series of 50 healthy controls. The voltage of R in the present series is less than in any reported by other authors, with the exception of Lewis and Gilder (1912) and less than in a series of 50 normal controls examined by us. In view of the elasticity of normal standards it is difficult to decide whether

TABLE I

COMPARISON OF THE VOLTAGE TO R IN RHEUMATOID ARTHRITIS WITH PUBLISHED DATA AND NORMAL CONTROLS

	Chamberlain and Hay (1939)	Hoskin and Jonescu (1940)	Larsen and Skulason (1941)	Wilson and Nyboer (1937)	Lewis and Gilder (1912)	Present study	
						Arthritis group	Control group
No. patients ..	302	50	100	104	52	60	50
Minimum							
R I	1·5	—	1·8	1·5	2·0	1·0	2·1
R II	3·6	—	4·1	4·0	5·5	2·0	2·0
R III ..	0·5	—	0·7	1·0	—	1·0	0·5
Maximum							
R I	18·6	—	12·4	19·4	12·0	17·0	14·3
R II	23·6	—	23·4	23·6	16·5	21·0	21·0
R III ..	20·5	—	20·8	20·0	13·5	14·0	20·2
Average							
R I	8·0	9·8	7·7	5·73	5·16	4·85	7·07
R II	12·7	13·5	10·2	11·90	10·32	8·61	9·28
R III ..	7·3	6·5	4·6	7·99	6·61	3·95	4·03

the above findings really show a tendency to lower voltage, in patients with rheumatoid arthritis.

Of the conditions associated with rheumatoid arthritis, anæmia (Turner, 1932; Szekely, 1940) and generalized wasting (Speckman and Rich, 1931; Steuer, 1934; Leach *et al.*, 1941) were found to coincide with low voltage. Considering that pericarditis is one of the known causes of low voltage, it is of interest that pericarditis was found at autopsy in a proportion of patients with rheumatoid arthritis by Baggenstoss and Rosenberg (1941 *a*, *b*) Bayles (1943), and Young and Schwedel (1944).

RADIOLOGICAL STUDY OF THE HEART IN RHEUMATOID ARTHRITIS

Published work on the heart in rheumatoid arthritis, as indicated above, deals chiefly with anatomical and clinical findings. Extensive search of the journals has failed to reveal a comprehensive radiological study. Rogen (1947) seems the only author who attempted cardiac X-ray examinations in some of his 33 rheumatoid arthritis patients, but gave it up because of difficulties in positioning, due to inability of the patients to stand upright.

Method. As it was intended to use heart size prediction tables based on height and weight, the 60 patients with rheumatoid arthritis in this series were selected from patients able to stand upright. In addition a control group of 100 patients, seen in the course of daily radiological routine by one of us (F.J.G.) was also investigated; they were selected to show an age distribution similar to the rheumatoid arthritis group, and patients with raised blood pressure were again excluded. Using prediction tables based on weight in patients in whom weight loss is a prominent feature, the possibility arose that the impression of cardiac enlargement might be produced where discrepancy between predicted and actual heart measurement was due to discrepancy between the patient's present and past weight. To test and minimize this source of error, the control group consisted of patients most of whom had shown considerable loss of weight.

The heart was examined by frontal teleradiogram and fluoroscopy including study of the barium-filled gullet. To determine heart size three standards were used.

(a) The transverse cardiac diameter was compared with prediction tables based on height and weight, as devised by Ungerleider and Clark (1939). Generally 80 per cent of normals fall within ± 10 per cent of the predicted transverse diameter; not more than 10 per cent exceed $+10$ per cent. This means that a few normal hearts are classified as being enlarged, and others with minor degrees of enlargement are not recognized. With these qualifications enlargement of the heart exists when the actual transverse measurement deviates from the predicted measurement by 10 per cent or more. (b) According to Comeau and White (1942) in the great majority of cases a transverse diameter greater than 13·4 cm. in males or 12·4 cm. in females is a sign of cardiac enlargement. Considered as a group the transverse diameter will be below 13·4 cm. in 90 per cent of normal males and below 12·4 cm. in 94 per cent of normal females. (c) In using radiological methods for estimating heart size the difficulty of applying mathematical methods to biological

problems must be remembered (Gwynne, 1933; Comeau and White, 1942). The diagnosis of cardiac enlargement was therefore made only if in addition to showing increased measurements, the cardiac silhouette was judged to be enlarged on inspection.

Table II shows that subjective judgment and measurement were not always in accord. That radiographic measurement alone should not be relied upon to diagnose cardiac enlargement is indicated by the fact that different hearts are shown as enlarged by different standards (Table II).

Heart Size. As measurements of heart size and subjective judgment (Table II) have given divergent results they will be discussed separately.

A transverse diameter of more than 10 per cent in excess of the predicted figure, was found in 15 patients (25 per cent) in the rheumatoid group, with only 8 per cent in the control series. In 8 patients (13 per cent) in the rheumatoid group the transverse diameter was 15 per cent or more in excess of the predicted figure, with not a single instance in the control series. The figure of 12·4 cm.

TABLE II

PATIENTS IN WHOM THE HEART WAS FOUND ENLARGED ACCORDING TO ONE OR MORE OF THE THREE STANDARDS EMPLOYED

Case No. and type of enlargement	Transverse cardiac diameter in excess of predicted +10% of 12·4 in women, 13·4 in men				Heart judged enlarged
	Predicted (cm.)	Actual (cm.)	Excess (percentage)	Actual (cm.)	
1	—	—	—	13·3 F	—
5 LA*	—	—	—	— F	—
6 LV,LA	11·9	13·2	11	13·2 F	+
7 G (Fig. 1) ..	—	—	—	14·0 F	++
9 LV	11·6	14·0	21	14·0 M	+
19 LV	11·6	13·1	13	13·1 F	+
20 LV (Fig. 2) ..	—	—	—	15·0 M	++
24 G (Fig. 3) ..	13·1	15·1	15	15·1 M	++
27	—	—	—	13·5 F	—
28	11·7	13·2	13	13·2 F	—
30	—	—	—	13·2 F	—
32 G	11·5	13·2	15	13·2 F	+
35 LV,LA (Fig. 4) ..	11·1	13·6	23	13·6 F	++
36 LV,LA	—	—	—	15·0 M	+
43 LV (Fig. 5) ..	11·7	14·0	20	14·0 M	++
46 LV (Fig. 6) ..	—	—	—	14·7 M	++
48 LV (Fig. 7) ..	13·6	15·6	15	15·6 M	++
51	11·8	13·5	11	13·5 F	—
53 G	11·6	14·5	25	14·5 F	+
56	10·9	12·3	13	— F	—
57	11·2	12·4	11	— F	—
58	10·4	11·7	13	— F	—
60 LV (Fig. 8) ..	11·2	13·1	17	13·1 F	++

* LV=enlargement mainly left ventricular. G=enlargement generalized. LA=left auricular enlargement causing gullet displacement. F=female. M=male. +=moderate enlargement. ++=pronounced enlargement.

Eight women with a transverse diameter between 12·5 and 13·0 cm., but with no other evidence of cardiac enlargement, are not included in this table.

Discrepancy was particularly obvious with regard to the standard of Comeau and White (1942); the number of hearts with transverse diameters in excess of their figures was strikingly high (45 per cent), while on inspection many appeared to be normal. For this reason the relation of each heart examined to this standard was recorded, but the result was not regarded as decisive in judging heart size in any given patient, although considered significant in group comparison.

in females and 13·4 cm. in males was exceeded by 27 patients (45 per cent), the corresponding figure in the control series being 10 per cent.

On inspection the heart was judged to be enlarged in 14 patients (23 per cent). Enlargement was regarded as pronounced in 8 (13 per cent), and moderate in 6 (10 per cent). The radiograms showing pronounced enlargement are reproduced in Fig. 1 to 8. Subjective judgment differed from that based on prediction tables. In Cases 7 and 46,

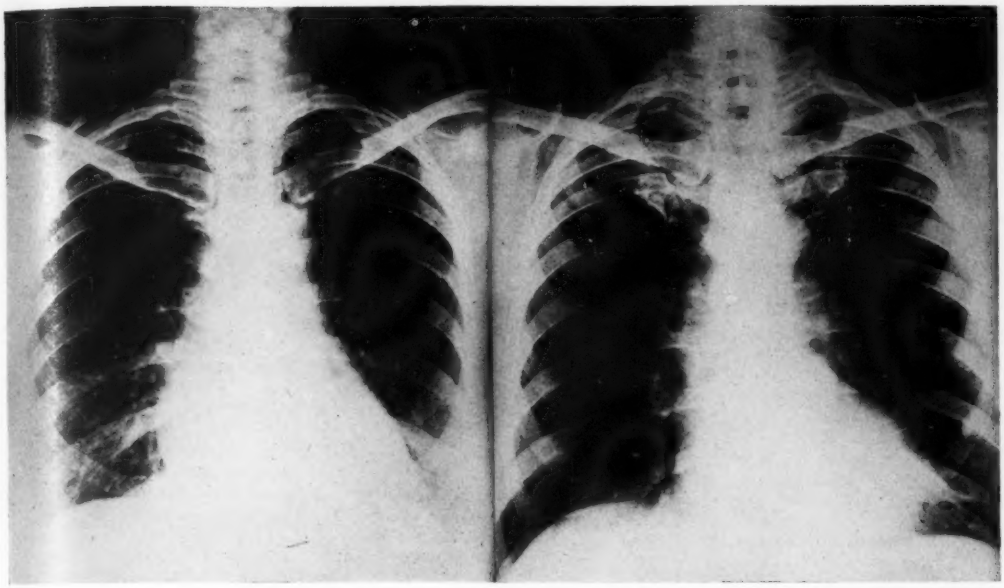

FIG. 1.—Case 7, female, 52 years. Generalized enlargement by inspection, although measurement at upper limit of predicted range. Clinically normal heart. Cardiogram normal.

FIG. 2.—Case 20, male, 63 years. Mainly left ventricular enlargement by inspection, although measurement at upper limit of predicted range. Clinically normal heart. Cardiogram normal.

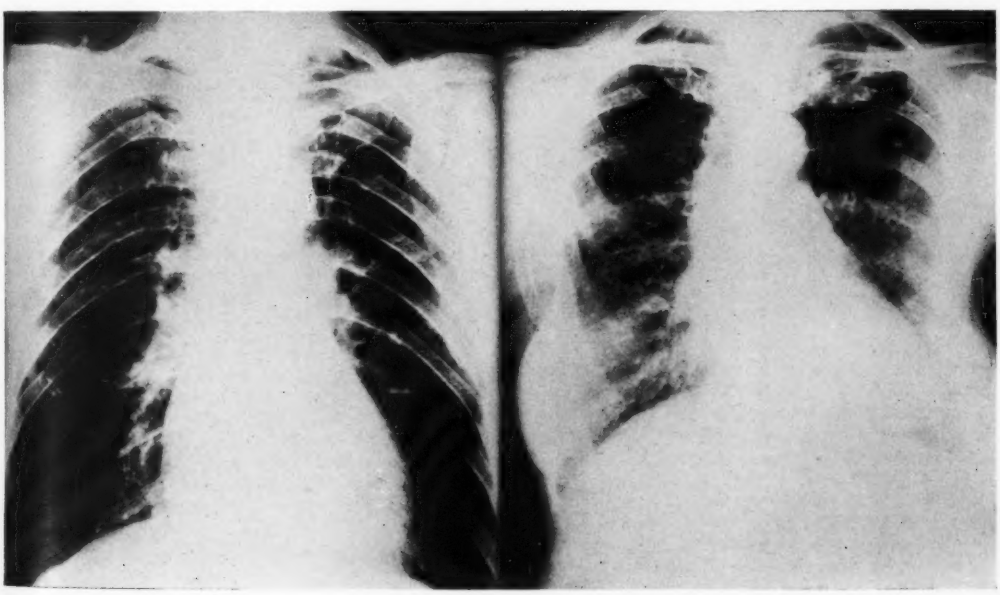

FIG. 3.—Case 24, male, 69 years. Generalized cardiac enlargement by inspection and measurement. Clinically normal heart. P–Q phase 0·22 sec.

FIG. 4.—Case 35, female, 63 years. Left auricular and left ventricular enlargement by inspection and measurement. Clinically moderate shortness of breath on exertion. Cardiogram normal.

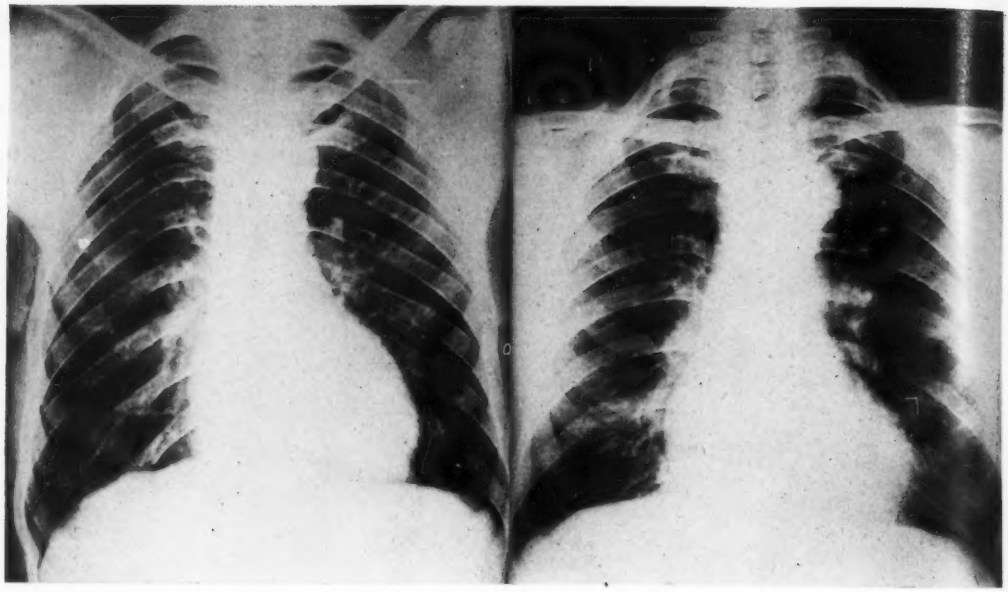

FIG. 5.—Case 43, male, 26 years. Mainly left ventricular enlargement by inspection and measurement. Heart clinically normal. Cardiogram normal.

FIG. 6.—Case 46, male, 46 years. Mainly left ventricular enlargement by inspection, although measurement at upper limit of predicted range. Clinically normal heart. Cardiogram normal.

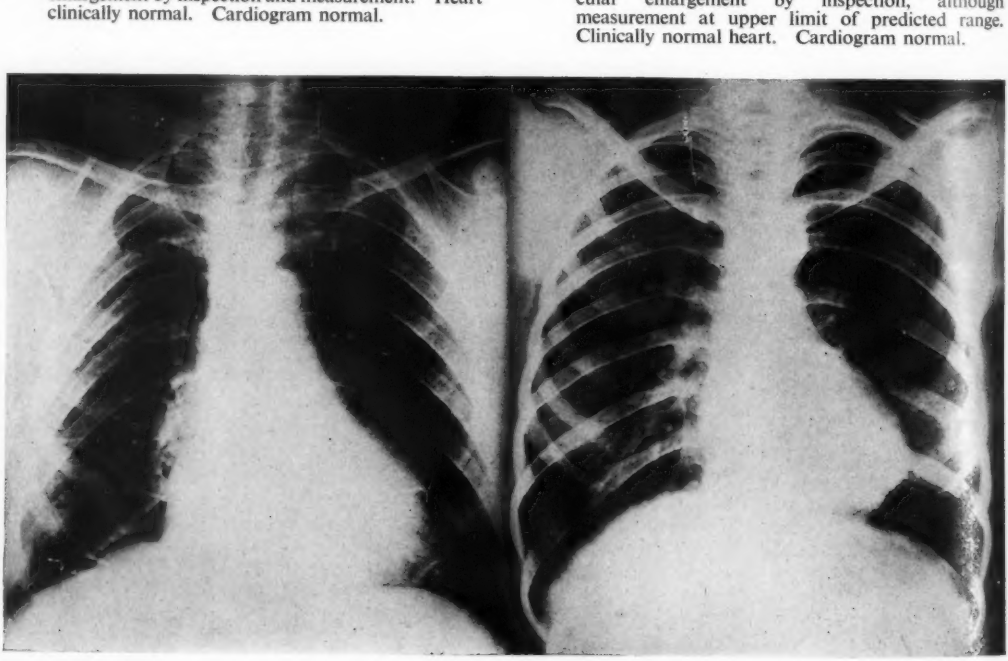

FIG. 7.—Case 48, male, 65 years. Mainly left ventricular enlargement by inspection and measurement. Triple rhythm with extra sound in mid-diastole, otherwise clinically normal. Normal cardiogram.

FIG. 8.—Case 60, female, 23 years. Mainly left ventricular enlargement. Palpitation and shortness of breath on moderate exertion, otherwise clinically normal. Normal cardiogram.

the actual transverse diameter was less than 10 per cent in excess of the predicted figure although on inspection pronounced enlargement was deemed to be present. On the other hand, of the patients whose transverse diameter was more than 10 per cent in excess of the predicted figure, 4 were not judged to be enlarged (Cases 28, 51, 56, 58). Of the 8 patients whose hearts were 15 per cent or more in excess of the predicted measurements all were judged to be enlarged, 3 moderately, and 5 considerably (Table II).

In clinical practice the radiological diagnosis of cardiac enlargement is usually made in a patient presenting signs and symptoms of a well-known heart disease and in most cases finally rests on a combination of radiological and clinical judgment. The situation is different here, a type of patient being examined in whom enlargement of the heart has not been demonstrated radiologically in the past, and who is suffering from a disease where the presence of cardiac involvement is regarded as questionable and is the unknown factor being investigated. Clinically these patients are characterized by the absence of signs or symptoms of heart disease. Pronounced cardiac enlargement such as is present in 8 patients in the present series can be diagnosed on radiological grounds alone. The diagnosis of slight to moderate enlargement on the other hand should be made only in the presence of supplementary evidence (Parkinson, 1933; Bramwell, 1933). Clinical manifestations of heart disease, which are the usual source of such evidence, are strikingly absent in patients with rheumatoid arthritis. It is suggested, on the other hand, that the evidence required to diagnose moderate cardiac enlargement in these patients is supplied from the following three sources.

Study of Patients as a Group. Prediction tables of heart size are composed of average figures derived from the study of large groups. The error involved in their use will therefore be smaller if applied to a group instead of to an individual. If in a single patient radiological determination of the transverse cardiac diameter in itself may not suffice to reveal the presence of *moderate* cardiac enlargement, in a group showing excessive measurements a tendency to cardiac enlargement may be assumed. In the single patient the impression of cardiac enlargement may be created or hidden by variations within the physiological range, in a group variations in the two directions will tend to neutralize each other. Comparison of the rheumatoid patients with the control group shows that a clear line of demarcation between patients with normal heart size and those with a tendency to enlarged hearts can be achieved by applying this method to groups instead of individuals.

Comparison with Anatomical Findings. Estimates of radiological enlargement in the present series are lower than the incidence rate of enlarged hearts reported at autopsy. Baggenstoss and Rosenberg (1941 *a*, *b*) found hearts of greater than normal weight in 11 of 25, Bayles (1943) in 13 of 23, and Young and Schwedel (1944) in 19 of 33 patients. These figures include cardiac enlargement due to rheumatic heart disease and to other causes, including hypertension. Considering that radiological heart size estimation will inevitably miss a number of moderately enlarged hearts, and that the present series did not include patients with hypertension, there is no obvious discrepancy between the autopsy and radiological data.

Radiologically revealed cardiac enlargement although in disharmony with the absence of clinical manifestations, is in keeping with the only positive group of facts we possess about the heart in rheumatoid arthritis, namely the findings at autopsy. Discrepancies between radiological and clinical findings would appear no more "startling" (Hench, 1941, referring to the anatomical findings) than the much discussed discrepancy between anatomical and clinical findings. The question arises here as to what extent these two in themselves independent discrepancies will serve to explain each other. In the absence of symptoms and signs radiological enlargement may be the only clinical manifestation of the changes found at autopsy.

Pronounced Cardiac Enlargement. Cardiac enlargement of a pronounced degree was found in 8 out of 60 patients with rheumatoid arthritis. In addition, 6 patients had hearts suggesting enlargement. By themselves these may not be regarded as evidence of frequent cardiac enlargement. If, however, an increased number of hearts are found to be at the upper limit of normal and 8, as compared with none in the control group, are found to be enlarged to a pronounced degree, the suggestion emerges that the hearts are actually increased in size in more than 8 out of 60 patients.

Radiological Configuration of Enlarged Hearts. Of the 8 considerably and 6 moderately enlarged hearts, left ventricular enlargement alone was found in 7, left ventricular and left auricular enlargement in 3, and generalized increase in size in 4. Left auricular enlargement alone was present in 1, and with left ventricular enlargement in 3 patients.

Predominantly right-sided enlargement was not seen in any of the hearts examined. It appears that the left ventricle is the chamber chiefly affected, and it was enlarged in every patient with an abnormal heart, excepting the one in whom left auricular enlargement was the only change present.

Discussion

The result of the above investigation suggests the *presence* of radiologically evident, mainly left ventricular cardiac enlargement in 23 per cent of patients with rheumatoid arthritis. On the other hand it appears that the cardiac abnormality underlying the enlargement is characterized by the *absence* of recognized clinical and electrocardiographic manifestations of heart disease.

In an attempt to explain this discrepancy, published reports regarding autopsy findings in rheumatoid arthritis will have to be taken into consideration. Three recent anatomical studies suggest that in patients with rheumatoid arthritis a disease of the heart is present which is "indistinguishable" from that found after

rheumatic fever (Baggenstoss and Rosenberg, 1941 *a*, *b*; Bayles, 1943; Young and Schwedel, 1944). The incidence of cardiac involvement in the three groups varies from 26 to 66 per cent, but unanimity exists with regard to certain points. It seems that the lesions found resemble rheumatic carditis more closely than any known cardiac lesion and that pericarditis, chronic or subacute myocarditis, gross valvular distortion and cardiac enlargement was present in a proportion of cases. The participation of the various chambers in the enlargement is not stated.

In addition to these changes, coronary sclerosis with or without myocardial infarction was found in a smaller proportion of patients in the three above groups. Coronary sclerosis as a cause of radiologically manifest cardiac enlargement in patients with rheumatoid arthritis is, in addition to its low incidence in the above three autopsy series, excluded by the following points. The role of coronary sclerosis alone in causing cardiac hypertrophy is still a matter of controversy. That it is able to cause enlargement is stated by Palmer (1937), denied by Jones (1930), Gross and Spark (1937), and Maun (1941). Clawson (1939) states that narrowing of the coronary orifices in syphilitic aortitis fails to produce hypertrophy in the absence of a valvular lesion. If only 1 out of every 2 or 3 patients with coronary sclerosis is expected to have an enlarged heart, to explain cardiac enlargement in 23 per cent, as found in the present series, it would have to be assumed that coronary sclerosis was present in 46 to 69 per cent. If coronary sclerosis were the chief cause of cardiac enlargement in rheumatoid arthritis, an increase of the incidence of cardiac enlargement with age could be expected. Table III shows that

TABLE III

INCIDENCE OF ENLARGED HEARTS DECREASING WITH INCREASING AGE

Age group Years	All rheumatoid arthritis cases	Transverse diameter 10% in excess of predicted		Heart judged enlarged	
		No.	Percentage	No.	Percentage
20–39	11	4	36	3	27
40–59	34	8	24	8	24
60–79	15	3	20	3	20
20–79	60	15	—	14	—

this is not the case, as the percentage of enlarged hearts actually decreases with age. In the control group only 8 per cent exceeded predicted cardiac measurements. Neither clinical nor cardiographic evidence of coronary sclerosis was demonstrated in the arthritic patients.

If coronary sclerosis is excluded, only the changes "resembling rheumatic carditis" occur with enough regularity to need consideration as the basis of the radiological cardiac enlargement. Whether these anatomical changes mean that rheumatic carditis is actually present, or whether they are an expression of rheumatoid arthritis ("rheumatoid carditis" Rosenberg *et al.*, 1944) is undecided. This problem is closely linked with the controversy regarding the relationship of rheumatic fever and rheumatoid arthritis. Since the ætiology of these two diseases is unknown, proof of their identity must be indirect, and either attempting to show the similarity of the conditions under which they occur, or the similarity of certain pathological and serological changes found in both. The two diseases tend to occur in identical families and individuals, and their geographic distribution and seasonal incidence is similar. The identity of the rheumatic nodule in the two diseases has been pointed out by Coombes and Coates (1926), Dawson (1933) and by Poynton and Schlesinger (1937), but questioned by Bennett *et al.* (1940). Immunological evidence suggests the presence of a streptococcal antibody in both diseases, but in rheumatic fever it is a lysin (Todd, 1932; Coburn and Pauli, 1932), in rheumatoid arthritis an agglutinin (Dawson *et al.*, 1934). The response to salicylates is different in the two diseases. Inflammatory granulomatous changes regarded as specific for rheumatoid arthritis, were found by Steiner *et al.* (1946) in muscle tissue obtained by biopsy. Similar changes were also found (Curtis and Pollard, 1940; Freund *et al.*, 1942) in the peripheral nerves. These changes were not demonstrated in rheumatic fever. The above data suggest that while evidence of the pathological and immunological identity of the two diseases is incomplete and in view of more recent investigations open to doubt, the two diseases tend to occur under similar circumstances, and in the same individual. For this reason, and because the cardiac changes described at autopsy in rheumatoid arthritis resemble rheumatic fever more closely than any other known cardiac disease, the possibility that the radiological enlargement is due to rheumatic carditis deserves attention.

If so, one must explain the discrepancy between the presence of the familiar clinical and radiological picture in chronic rheumatic carditis and its absence in these patients. This need still exists, if the anatomical changes are an expression of "rheumatoid carditis," because, regardless of ætiology, it is still not explained why gross cardiac disease remains without symptoms or signs.

The heart disease assumed to be present in rheumatoid arthritis is characterized by the presence of left ventricular enlargement, and the absence of gross congestive heart failure, acoustic abnormalities, auricular fibrillation, and cardiographic changes.

The absence of congestive failure is partly explained by assuming a milder myocardial process due to three causes. (1) A difference in the age at onset, which will alter the course of these two forms of heart disease owing to the greater sensitivity of the heart in youth to the rheumatic agent (Poynton and Schlesinger, 1937; Sangster, 1940; De Liee *et al.*, 1943), and the greater capacity of the young heart muscle to hypertrophy (Palmer, 1937). Hypertrophy, although initially increasing the efficiency of the heart eventually becomes a liability. (2) A reduction of physical performance of the patient due to joint involvement. Available evidence suggests that the progression and outcome of rheumatic heart disease is influenced by the amount of rest and

exercise during its course. (3) More gradual development of the rheumatic process. This would allow for smoother adjustment of the heart to the changes in circulatory dynamics.

The assumption of a milder form of cardiac disease is in keeping with the statement by Rosenberg *et al.* (1944) that the cardiac lesion associated with rheumatoid arthritis is not as severe or widespread as such a lesion in young persons who have rheumatic fever, and also with the fact that in the present series of patients with rheumatoid arthritis, radiologically evident cardiac enlargement, although frequently present, was in most cases not excessive.

There are two possible contributory causes of the absence of abnormal sound phenomena: (1) A milder myocardial process. Triple rhythm due to rapid diastolic inflow is the only acoustic abnormality in heart disease of the rheumatic carditis type, the absence of which may be explained on this basis, since it usually accompanies advanced disease (Weber, 1937; Evans, 1943). (2) Physical properties of the blood. The incidence and intensity of other murmurs here being considered is not dependent on the extent of cardiac involvement. If as we are informed by those who investigated such hearts anatomically valvular and muscular changes are identical in the two conditions, the question arises, whether the physical state of the blood accounts for some of the differences. Estimation of blood velocity and the B.M.R. in ten patients in this series gave normal results, nor did significant murmurs appear when blood velocity was increased by exertion. Information regarding the kinematic viscosity of full blood in rheumatoid arthritis is so far not available and is being studied at present by Sagar and Fischmann (1947).

Left ventricular enlargement was found in this series, instead of the characteristic cardiac silhouette of rheumatic valvular disease. In chronic rheumatic carditis the distribution of dilatation and hypertrophy of the cardiac chambers is determined by the combined effect of the inflammatory lesion and the distribution of mechanical strain, the latter according to the localization of the pathological process in the valves. In rheumatoid arthritis, on the other hand, with the lessening of physical exertion the importance of the mechanical factor will diminish and the distribution of enlargement will follow chiefly, or alone the distribution of the inflammatory process. In rheumatic carditis Gross and Erhlich (1930) found that Aschoff bodies were almost invariably present in the interventricular septum and the posterior wall of the left ventricle, while other parts of the heart were less frequently invaded. Also the enlargement of the heart found in patients dying in the early stages of rheumatic carditis is largely limited to the left ventricle (Boyd, 1931).

Summary

The 60 rheumatoid arthritis patients in this series were selected to have normal blood pressure, no history of rheumatic fever, and no chest deformity, and to be able to stand upright for cardiac radiography.

Clinical and electrocardiographic findings were negative apart from a tendency to low voltage of the standard leads.

Radiological examination suggested the presence of cardiac enlargement in 23 per cent of patients. Enlargement was left ventricular in 50 per cent of these, left ventricular and left auricular in 21 per cent, generalized in 29 per cent, and right sided in none of the hearts judged enlarged. The gullet was displaced backward at the level of the left auricle in 29 per cent of enlarged hearts.

It is thought probable that radiologically manifest cardiac enlargement in rheumatoid arthritis is an expression either of chronic rheumatic carditis or a form of cardiac involvement due to the ætiological factor of rheumatoid arthritis.

An attempt is made to explain the prevalence of the left ventricle in cardiac enlargement and also the absence of clinical and electrocardiographic manifestations of heart disease in the presence of radiologically demonstrated enlargement.

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ABSTRACTS OF CARDIOLOGY

Physiological Studies in Congenital Heart Disease. I. Procedures. R. J. BING, L. D. VANDAM, and F. D. GRAY. *Bull. Johns Hopk. Hosp.*, **80**, 107–120, Feb., 1947.

The technical aspects of physiological studies of cases of congenital heart disease are described. The procedures and formulæ mentioned are those dealing with the measurement of blood flow in the pulmonary artery, systemic circulation, pulmonary capillary bed, and intracardiac shunts. In all, 14 formulæ are presented, including one for measuring the peripheral resistance. The techniques used involve the evaluation of oxygen and carbon dioxide in arterial and venous blood and also in blood collected by intracardiac catheterization, together with determination of the rates of oxygen consumption and carbon dioxide elimination by indirect calorimetry.

[This paper cannot easily be abstracted, and those interested in the subject are advised to consult the original communication.] *A. I. Suchecki*

Physiological Studies in Congenital Heart Disease. II. Results of Preoperative Studies in Patients with Tetralogy of Fallot. R. J. BING, L. D. VANDAM, and F. D. GRAY. *Bull. Johns Hopk. Hosp.*, **80**, 121–141, Feb., 1947.

This paper deals with results of pre-operative studies on patients with cardiac abnormalities and in whom a reduced pulmonary blood flow is an important feature. Altogether 120 patients with the tetralogy of Fallot have been investigated. Here there is an intracardiac shunt from right to left. However, there may be some concomitant flow from left to right, as indicated by a higher oxygen content of right ventricular blood as compared with that of the right auricle. In some cases both systemic and pulmonary artery flows are equally reduced below normal values: the intracardiac shunt is negligible and the aorta rises chiefly from the left ventricle. With varying degrees of pulmonary stenosis and ventricular septal defect, the systemic blood flow depends to a large extent on the importance of the intracardiac shunt. The total pulmonary flow (pulmonary capillary flow) approaches closely the volume of pulmonary artery flow normally and rarely in the tetralogy of Fallot, indicating in the latter absence of measurable collateral circulation. In the majority of patients with pulmonary stenosis, however, pulmonary capillary flow exceeds pulmonary artery flow, suggesting the presence of an important collateral circulation to the lungs. In 4 patients with pulmonary stenosis and patent ductus arteriosus the volume of blood flow through the ductus could be determined by measuring the difference between the pulmonary capillary and pulmonary artery flows.

It has been shown directly, by intracardiac catheterization, that the systolic pressure in the right ventricle in cases of the tetralogy is above normal and approximates to the systolic pressure in the systemic circulation. In 8 out of 22 recordings the general level of the ventricular diastolic pressure was also elevated. When the catheter is passed into the stenosed pulmonary artery the pressure falls sharply. In 3 subjects the systolic pressures in the right ventricle and in the aorta were similar.

In the tetralogy of Fallot the oxygen consumption is decreased and this, the authors suggest, is the result of physiological adaptation to chronic anoxia. The decreased metabolic rate may also be due to a poor nutritional status, lack of physical activity, or poor calorie intake. The ratios of oxygen consumed and carbon dioxide produced decreased during the standard exercise test, while the arterial oxygen saturation dropped immediately after the exercise. This exercise test might be of diagnostic help. Finally, the authors stress the interrelationship of venous-arterial shunts and decreased pulmonary blood flow in the production of anoxæmia. The volume of " effective pulmonary blood flow " is the determining factor. *A. I. Suchecki*

Physiological Studies in Congenital Heart Disease. III. Results Obtained in Five Cases of Eisenmenger's Complex. R. J. BING, L. D. VANDAM, and F. D. GRAY. *Bull. Johns Hopk. Hosp.*, **80**, 323–347, June, 1947.

Physiological methods have been used to study the circulation in the heart and great vessels in 5 cases of Eisenmenger's complex. Clinically these cases can be distinguished from those of Fallot's tetralogy because the cyanosis and clubbed fingers develop later in life, though breathlessness on exertion is present from childhood. The patient also suffers many hæmoptyses, and a loud systolic murmur is audible over the base of the heart close to the left of the sternum. Radioscopy shows a prominent pulmonary conus, marked vascular root shadows, and expansile pulsations in the lung fields. Such cases are not at present amenable to surgical treatment.

In 4 or 5 such cases exercise was accompanied by a rise in the ratio of oxygen consumed per litre of ventilation, whereas in patients with the tetralogy of Fallot the ratio usually declines. The preponderant shunt of blood was from the left to the right ventricle in 3 cases and from right to left in 2, though in all there was interventricular mixing of blood. The authors believe that there is an increased resistance in the pulmonary bed in these cases, because there was no marked tendency for the blood to flow from left to right and because the pulmonary arterial pressure was increased. The calculated work of the

right ventricle was 30 to 50% of that of the whole heart, whereas it is usually 15% and the ratio velocity energy/total work, when calculated for the right ventricle, was only one-tenth of the normal. It is pointed out that in some cases of septal defects in infants generalized narrowing of the pulmonary arterioles due to thickening of the media and intima has been found, and similar changes have been described in 2 cases of large interauricular septal defect. These post-mortem findings appear to tally with the ante-mortem finding of increased pulmonary vascular resistance. *H. E. Holling*

Studies of Congenital Heart Disease. I. Technique of Venous Catheterization as a Diagnostic Procedure. L. DEXTER, F. W. HAYNES, C. S. BURWELL, E. C. EPPINGER, R. E. SEIBEL, and J. M. EVANS. *J. clin. Invest.*, **26**, 547–553, May, 1947.

This paper, the first of a series of three, deals with the application of intracardiac catheterization to the study and diagnosis of congenital heart disease. The method described by the investigators is that introduced by Cournand and his associates for the study of hæmodynamics. Several samples of blood from the right cardiac chambers and pulmonary artery and vena cava are collected and examined for oxygen content; in addition, blood from the femoral artery and oxygen consumption are studied. The data obtained can be utilized for the calculation of blood flow in patients with congenital heart disease (Fick's formula). The volume of flow through single one-directional shunts may most easily be estimated by calculating the difference between the pulmonary and peripheral flows. The estimation becomes more difficult when double shunts, shunts in both directions, and collateral circulation are present. The authors give details of estimation of the blood pressure in the pulmonary artery, right ventricle, and right auricle. A continuous pressure curve can be recorded during the withdrawal of the catheter from the pulmonary artery through the right cardiac chambers. The method of intracardiac catheterization, as already shown by others, carries no danger. In a few patients ventricular extrasystoles and auricular fibrillation have been noted, but these, as well as a venous spasm occasionally seen, are transient. Of 42 patients, only 1 presented symptoms troublesome enough to require interruption of the procedure. *A. I. Suchecki*

Studies of Congenital Heart Disease. II. The Pressure and Oxygen Content of Blood in the Right Auricle, Right Ventricle, and Pulmonary Artery in Control Patients, with Observations on the Oxygen Saturation and Source of Pulmonary "Capillary" Blood. L. DEXTER, F. W. HAYNES, C. S. BURWELL, E. C. EPPINGER, R. P. SAGERSON, and J. M. EVANS. *J. clin. Invest.*, **26**, 554–560, May, 1947.

This communication deals solely with results of intracardiac catheterization performed in control patients known to have no congenital cardiac defect. The blood pressures in each chamber have been recorded, and there seems to be little difference between pulmonary artery and right ventricle pressures: this normal finding contrasts with that in pulmonary stenosis, where the systolic ventricular pressure is clearly higher than that in the pulmonary artery. In some congenital heart conditions, left to right shunt introduces arterial blood into the right chambers, thereby increasing the oxygen content of blood in the latter. What, then, are the normal variations in oxygen content in the right heart? The results in the controls show that the greatest increase in oxygen from the superior vena cava to the right auricle is 1·9 vol.%; from the right auricle to the right ventricle, 0·9 vol.%; and from the right ventricle to the pulmonary artery, 0·5 vol.%. Within each chamber variation of oxygen content occurs; it is minimal in the pulmonary artery. It is suggested by the authors that blood from the pulmonary artery be employed for the determination of oxygen content in mixed venous blood for use in Fick's formula. Lastly, by comparing the oxygen values of a sample of blood obtained through the catheter obstructing a small branch of the pulmonary artery with that from the femoral artery, the investigators have shown that the former blood originates in the pulmonary capillary and venous bed rather than in pre-capillary anastomoses with systemic arteries. *A. I. Suchecki*

Studies of Congenital Heart Disease. III. Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosis, Tetralogy of Fallot, Ventricular Septal Defect; and Auricular Septal Defect. L. DEXTER, F. W. HAYNES, C. S. BURWELL, E. C. EPPINGER, M. C. SOSMAN, and J. M. EVANS. *J. clin. Invest.*, **26**, 561–567, May, 1947.

The authors describe intracardiac catheterization as a diagnostic aid in 7 patients with four varieties of congenital heart disease: (1) Patent ductus arteriosus: the oxygen content of the blood in the pulmonary artery was, in 1 patient, 2·2 vol.% higher than that from the right ventricle. This is taken as direct evidence of entry of arterial blood into the pulmonary artery; a less constant finding is an elevation of blood pressure in the pulmonary artery and the right ventricle. (2) Tetralogy of Fallot: pulmonary stenosis was recognized by finding a higher systolic pressure in the right ventricle than in the pulmonary artery, and a narrow pulse pressure in the latter. In another case the intracardiac catheter passed from the right ventricle to the aorta, thus demonstrating a ventricular septal defect. (3) Interventricular septal defect (Roger's disease): in 1 case the blood in the right ventricle was found to be more highly oxygenated than that in the right auricle. (4) Interauricular septal defect: cases may be diagnosed by introducing the catheter into the left auricle through the septal defect, or by finding a significant increase in the oxygen content of blood in the right auricle (left to right shunt). In 1 such case a large increase of oxygenation of blood in the right auricle was found as compared with that of the superior vena cava (more than 1·9 vol.%); the value was practically identical with that found in the femoral artery. Similar findings to those in group 4 can be seen in tricuspid insufficiency associated with interventricular septal defect, and in the rare cases where a pulmonary vein empties into the right auricle. *A. I. Suchecki*

Venous Catheterization of the Heart. I. Indications, Technics, and Errors. M. C. SOSMAN. *Radiology*, **48**, 441–450, May, 1947.

Catheterization of the right heart is most useful in the study of hæmodynamics and in helping to establish an accurate diagnosis in congenital heart disease. In addition, the method has been used in the study of cerebral, renal, and hepatic physiology, in order to collect samples of blood directly from the jugular, renal, and hepatic veins.

From the median basilic vein in either antecubital fossa the catheter, made of woven silk, is passed upward into the axillary vein, the superior vena cava, and the right auricle. From there it may be guided into the right ventricle or, as the patient takes a deep breath, into the inferior vena cava, thence into either renal vein or into one of the hepatic veins. The direction of the tip of the catheter is controlled under intermittent fluoroscopic vision by twisting its proximal end. The tip moves with each cardiac pulsation, slightly in the auricle but much more so when the right ventricle is entered. From the right ventricle the catheter may be guided into either right or left pulmonary artery. Clotting of blood in the catheter is prevented by continuous perfusion of normal saline.

All patients have a test of basal metabolism before catheterization to determine their oxygen consumption. Arterial blood is withdrawn under oil by puncture of the femoral artery, for determination of arterial oxygen saturation. In patients with congenital heart disease, samples of blood are withdrawn from the pulmonary artery, right ventricle, right auricle, and superior vena cava, and films are taken of the catheter tip in each position. Peripheral blood flow is calculated by the direct Fick principle of dividing the oxygen consumption by the arteriovenous oxygen difference between the femoral artery and the right heart. Pulmonary flow may be estimated by dividing the oxygen consumption by the difference in oxygen content of the pulmonary artery and the femoral artery. The value of teamwork is stressed.

Examination was unsatisfactory in 13 out of 100 patients tested; causes for failure included unsatisfactory veins, spasm of vein around the catheter, kinking of an unsatisfactory catheter, and unco-operative patients. General anæsthesia is indicated only in young children. Extrasystoles were sometimes noted as the tip of the catheter passed through the tricuspid valve. In only two instances were subjective symptoms distressing enough to cause abandonment of the procedure. No evidence of thrombus formation or of damage to the endothelium of the large veins or heart has been found. Cournand has reported 1200 such examinations without fatality or serious complications from passage of the catheter.

Several radiographs, illustrating "normal" and abnormal or accidental positions of the catheter tip, add to the interest of this paper. Thus the tip is seen in an azygos vein, in an additional left-sided superior vena cava, in a coronary venous sinus, in a right-arched aorta, and (through an auricular septal defect) in a pulmonary vein. *T. Semple*

Venous Catheterization of the Heart. II. Results, Interpretations, and Value. L. DEXTER. *Radiology*, **48**, 451–462, May, 1947.

This paper discusses diagnostic aid obtainable in congenital heart disease by previous abstract. In auricular septal defect the catheter may be introduced through the defect or arterial blood may be found in the right auricle. The recognition of an uncomplicated interventricular septal defect depends on finding a significantly higher oxygen content of blood in the right ventricle than in the right auricle. In the tetralogy of Fallot the venous catheter may pass through the stenosed pulmonary valve into the pulmonary artery, where the pressure would be lower than that of the right ventricle, or it may pass through the septal defect and go directly into the overriding aorta. In patent ductus arteriosus, blood from the pulmonary artery has a higher oxygen content than that from the right ventricle.

With the aid of line drawings and serial radiographs the passage of the catheter is demonstrated from the superior vena cava to various positions in the representative types of cogenitally abnormal heart.

T. Semple

Experimental Serum Carditis and its Relationship to Rheumatic Fever. E. F. MCKEOWN. *J. Path. Bact.*, **59**, 547–555, Oct., 1947.

It has been reported by other workers that cellular infiltrations in the heart like those of rheumatic carditis have been found in 2 fatal cases of serum sickness; and that polyarteritis, like the occasional polyarteritis nodosa which may complicate rheumatic fever, may be a result of sensitization. Cardiac lesions, which show many of the histological characters of the rheumatic lesion, may also be found in the experimentally sensitized animals. The work here reported is an attempt to verify these experimental observations.

Rabbits were given 10 ml. of horse serum per kg. body weight intravenously or intraperitoneally: 17 days later 1 ml. of serum was injected intravenously to absorb circulating antibody: 2 days later the initial dose of serum was repeated; 1 week later, and in some instances after longer intervals, the animals were killed. The vascular lesions described could be found after a single injection of serum, but were more widespread in animals receiving a second dose. They were present in 88% of the animals; the coronary arteries were most often affected. The histological appearances of an inflammatory exudate surrounding and infiltrating the vessel are fully described.

Small granulomata closely resembling the Aschoff nodule of rheumatic fever were often found in the myocardium. Inflammatory nodules were also found in the endocardium, leading to fibrotic thickening. Similar lesions were found in the mitral valve and valve ring, less frequently in the aortic and tricuspid valves, and never in the pulmonary valve. The author believes that in histological structure and in site these experimental lesions are identical with those of rheumatic fever, and concludes that hypersensitivity is probably the essential mechanism in the production of the rheumatic lesion.

Kenneth Stone

New Test for Hypertension due to Circulating Epinephrine. M. GOLDENBERG, C. H. SNYDER, and H. ARANOW. *J. Amer. med. Ass.*, **135**, 971–976, Dec. 13, 1947.

The only clinically significant type of hypertension due to circulating adrenaline results from phæochromocytoma. It is suggested that this tumour may be much more common than is generally realized. The diagnosis is dependent on: (1) the typical syndrome of paroxysmal hypertension with signs of vasoconstriction, pallor, headache, vomiting, and tachycardia; hypertension may sometimes be persistent; (2) demonstration of the tumour by perirenal insufflation of air; this may not succeed as there are other sites in which chromaffin tissue may occur; (3) demonstration of circulating adrenaline in the blood, but this may be very difficult. The principle of the new procedure described is that hypertension due to circulating adrenaline will be abolished by the injection of adrenolytic compounds; hypertension due to any other cause will persist. Benzodioxanes in tolerable doses are adrenolytic only, and not sympathicolytic. Piperidyl methyl benzodioxane was used in a dose of 0·25 mg. per kilo intravenously. In cases of phæochromocytoma the injection of benzodioxane was followed by a fall in blood pressure which lasted for several minutes in 3 out of 4 cases. In the fourth the pressure fall was slighter. The diagnosis was confirmed at operation in all these cases. In patients with essential hypertension the blood pressure usually rose after benzodioxane, but rarely a slight and less significant fall of pressure took place. Benzodioxane produced some side-effects, such as tachycardia, flushing, palpitation, coldness of limbs, and dizziness. Fourteen patients found it unpleasant, while 44 were undisturbed by the test. *J. McMichael*

Studies on Plant Hypertensinase. F. GOLLAN, E. RICHARDSON, and H. GOLDBLATT. *J. exp. Med.*, **87**, 29–39, Jan. 1, 1948.

The extraction of hypertensinase from wheat bran is described. A preparation free from renin and with low toxicity was produced. This was found to cause a rise in plasma hypertensinase when injected intravenously into dogs but not when injected intramuscularly. The reaction of these animals to injections of hypertensin or renin was less marked. In dogs with experimental hypertension the blood pressure was reduced by intravenous hypertensinase, while the plasma hypertensinase level remained high, though hypertensin could be detected in the plasma. These effects were not produced by inactivated hypertensinase. *Majorie Le Vay*

Spinal Nerve Root Pain (Radiculitis) Simulating Coronary Occlusion: A Common Syndrome. D. DAVIS. *Amer. Heart J.*, **35**, 70–80, Jan., 1948.

More careful investigation of some cases diagnosed as coronary thrombosis reveals that they are really cases of spinal nerve root pain. The author describes 10 such patients who were under his care during 1946. The patients had described præcordial pain coming on in attacks and radiating either to the left arm or to the jaw, but a more careful probing of the history revealed that the pains might come on in bed, after there had been certain movements of the spine, or after such acts as coughing, sneezing, or straining at stool. Pressure over the dorsal vertebræ might provoke an attack, and tenderness in the region of the costo-chondral junctions might be elicited. The diagnosis can be confirmed by the beneficial response to postural correction and manipulation of the cervico-dorsal spine. Cervico-dorsal radiculitis may also coexist with coronary disease. Recognition of the syndrome and differentiation from coronary disease may prevent much unnecessary invalidism. *H. E. Holling*

Vitamin E in Angina Pectoris. D. H. MAKINSON, S. OLEESKY, and R. V. STONE. *Lancet*, **1**, 102, Jan. 17, 1948.

Twenty-two patients with typical angina of effort were treated with vitamin E, phenobarbitone, aminophylline, and calcium lactate, each drug being given for 3 weeks, after which the patients were asked to compare the effects of the drugs. From this small but clinically significant series it is concluded that vitamin E is not of any therapeutic value in the routine treatment of angina pectoris. —[Authors' summary.]

The Use of Dicumarol in Experimental Coronary Occlusion. I. The Ineffectiveness of Dicumarol when Ligation is the Method of Occlusion. E. J. BEATTIE, E. C. CUTLER, M. FAUTEUX, T. D. KINNEY, and H. D. LEVINE. *Amer. Heart J.*, **35**, 94–105, Jan., 1948.

The descending branch of the left coronary artery was crushed or ligated in 40 healthy dogs. Ligation was found to be a more certain way of producing an infarct, and for various reasons only 22 of the ligation experiments were found to be suitable for inclusion in the study. One group of these dogs was given adequate doses of dicoumarol after the ligation; a control group received no dicoumarol. The electrocardiographic and pathological changes were studied in both groups and no significant differences were found. Before applying these results to experience with human cases of coronary occlusion the limitations of the experiments must be borne in mind: (*a*) The coronary arteries of these dogs were healthy and therefore less likely to be the seat of an extensive thrombosis than the coronary artery of patients. (*b*) The experiments produced abrupt and total occlusion whereas in clinical coronary thrombosis the occlusion may be gradual. (*c*) Hæmorrhage after the operation was the cause of death in 3 of the dogs receiving dicoumarol and this factor would not operate in clinical work. (*d*) The number of satisfactory experiments is too small for statistical analysis. *H. E. Holling*

Rupture of the Heart Following Acute Myocardial Infarction. R. S. DIAZ-RIVERA and A. J. MILLER. *Amer. Heart J.*, **35**, 126–133, Jan., 1948.

Rupture of the heart occurred in 5 of 147 cases of myocardial infarction coming to necropsy; all 5 cases were from a group of 53 in which the infarction was acute. Rupture of the interventricular septum had been recognized ante mortem by the anginal pain followed by

the sudden appearance of a systolic murmur and the electrocardiographic changes typical of myocardial infarction and right axis deviation. In every instance of rupture of the left ventricle, clotting of the blood in the pericardium had occurred, and it was evidence that cardiac rupture resulting from acute myocardial infarction was not a cause of instantaneous death.

H. E. Holling

Treatment of Angina Pectoris by Reduction of Basal Metabolism. G. SCHOENEWALD. *Brit. med. J.*, **1**, 251–253, Feb. 7, 1948.

The author divides cases of angina pectoris into three groups—obese, anæmic, and slim. Patients in the first two groups can be helped by weight reduction and by correction of anæmia respectively; those in the third group can be given nitroglycerin to shorten their attacks. Commenting on total surgical removal of the thyroid gland, which has not been widely practised in Britain, the author describes 3 patients treated ambulantly with methylthiouracil. All were given 600 mg. daily for several weeks, with improvement in each case. It is noted that in order to reduce thyroid activity it is necessary to give much larger doses for a longer period to patients with normal thyroid activity than to those with thyrotoxicosis.

Geoffrey McComas

The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy. G. B. MYERS, H. A. KLEIN, and B. E. STOFER. *Amer. Heart J.*, **35**, 1–40, Jan., 1948.

The electrocardiographic criteria for the diagnosis of right ventricular hypertrophy have been reconsidered. A critical review of the literature is presented. Forty cases of right ventricular hypertrophy proven at necropsy were carefully studied. The authors find, as previous workers have shown, that right axis deviation in the standard leads, with depression of RST2 and RST3 and with inversion of T1 and T2, is not diagnostic of right ventricular hypertrophy. This pattern may be found in left ventricular hypertrophy and even in normal subjects when the heart is in a vertical position. [For the electrocardiographic features now considered typical of right ventricular hypertrophy the original paper must be consulted.]

H. E. Holling

Effect of Increasing the Blood Volume and Right Atrial Pressure on the Circulation of Normal Subjects by Intravenous Infusions. J. V. WARREN, E. S. BRANNON, H. S. WEENS, and E. A. STEAD. *Amer. J. Med.*, **4**, 193–200, Feb., 1948.

A series of normal young subjects were given intravenous infusions of normal saline or 5% human serum albumin in normal saline. The amounts ranged from 750 to 1,825 ml. and were given at rates ranging from 32 to 72 ml. per minute. The increase in blood volume consistently caused a rise in right auricular pressure, but cardiac output, arterial blood pressure, and pulse rate showed no consistent changes. Variations in auricular pressure of about 125 mm. water produced no demonstrable changes in the transverse diameter of the heart. It is concluded that increasing the blood volume and auricular pressure throws no demonstrable burden on the circulation of normal subjects. It is suggested: (*a*) that this may also be true of patients with cardiac failure; (*b*) that in them acute pulmonary œdema is precipitated by intravenous infusions because certain factors operate to cause a large portion of the administered fluid to accumulate in lungs already moderately œdematous.

R. T. Grant

Experiences in the Management of Subacute Bacterial Endocarditis Treated with Penicillin. P. A. TUMULTY and A. McG. HARVEY. *Amer. J. Med.*, **4**, 37–54, Jan., 1948.

Of 35 patients suffering from subacute bacterial endocarditis who were treated with penicillin 22 recovered; of these 12 remained well over periods of 3 to 36 months, 7 had some, usually mild, cardiac symptoms, one suffered from increasing heart failure, one died of cardiac and renal failure 5 months after the conclusion of treatment, and another died, after 6 months, in a mental hospital; the cause of death in the last case could not be ascertained by the authors. These patients had received penicillin treatment for 13 to 100 days, the amounts given daily varying between 200,000 and 18,000,000 units, with totals of 3,500,000 to 1,450,000,000 units. Of the 13 patients who did not recover only 4 were regarded as having received adequate treatment with penicillin; the cause of death in most of them was cardiac failure and embolism. Two died of myocardial infarction, which, in one case, was caused by a mycotic aneurysm of a coronary artery and in the other by coronary thrombosis.

The authors stress the difficulty of clinical diagnosis in the frequent absence of the classical signs, and the importance of retaining and reviewing blood cultures for 3 weeks before discarding them as sterile. The possibility of unusual causative organisms, such as the genus *Bacteroides*, is to be kept in mind. The authors consider as a "basic and minimal treatment schedule" 100,000 units of penicillin 2-hourly for 8 weeks, and assess satisfactory response mainly on clinical criteria, such as return of temperature and pulse rate to normal, improved appetite, and general well-being. If necessary, the dose of penicillin must be increased until satisfactory response is obtained. As a prophylactic measure against the development of subacute bacterial endocarditis in patients who suffer from valvular or congenital heart disease, the administration is recommended of at least 500,000 units of penicillin a day for 4 days in the case of dental extractions or other surgical procedures and manipulations which are likely to produce a transient bacteriæmia.

B. Samet

Effect of Tetraethyl Ammonium Chloride on a Mixed Type of Hypersensitive Carotid Sinus Syndrome. R. D. TAYLOR, L. C. UNDERWOOD, and I. H. PAGE. *J. Lab. clin. Med.*, **32**, 1491–1495, Dec., 1947.

The effect of the intravenous injection of atropine and of tetraethyl ammonium chloride was observed in a patient in whom pressure on the carotid sinus provoked bradycardia, fall in blood pressure, giddiness, and

syncope. Atropine prevented the slowing of the pulse rate but not the fall in blood pressure. Tetraethyl ammonium chloride prevented both the bradycardia and hypotension. The inhibition of the vegetative system by tetraethyl persisted for only 30 to 40 minutes, and the drug is therefore not recommended for treatment of this type of case. *R. T. Grant*

Hypertensive Vascular Disease: Duration of Life in a Selected Series. D. W. BLOOD and G. A. PERERA. *Amer. J. Med.*, 4, 83–88, Jan., 1948.

In order to assess the prognosis in cases of "benign," hypertension 50 patients were studied who, when first seen, had not significant symptoms but consistently had blood pressures of over 140/90 mm. Hg. Their ages varied from 22 to 57, the average being 42, and 41 were females and 9 males. The average length of observation was 17 years and varied from 10 to 27 years. Sixteen patients died, the majority as a result of cardiovascular complications or cerebral vascular accidents; 24 were free from significant symptoms when last seen. It was not possible to correlate prognosis with initial height of blood pressure, symptoms of headache or palpitation, the presence of cardiac enlargement, albuminuria, minor electrocardiographic changes, or retinal arterio-venous compression. Symptoms of cardiac failure appeared late in the course of the disease; 8 of the 22 patients developing such symptoms died after an average of 8 years from the first symptom. On the other hand, only one of the 9 patients developing cardiac pain survived, the average duration of life from the onset of pain being 5 years.
C. Bruce Perry

Severe Hypertension in Young Persons. A Study of 50 Cases. R. PLATT. *Quart J. Med.*, 27, 83–93, Jan., 1948.

As a result of investigation into the cause of 64 cases (14 more are contained in an addendum) of severe hypertension in patients under the age of 40, the author concludes that the impression that one of the outstanding features of malignant hypertension is its frequent occurrence in young adults and even in children, is erroneous. Although he did not personally select his cases, he is careful to point out that as his interest in this subject is known by practitioners he has been sent a disproportionate number of rarities. He emphasizes the great difficulty of distinguishing essential hypertension from hypertension due to demonstrable causes, and states that at times the diagnosis cannot be made with certainty even microscopically. For example, it may be impossible to distinguish atrophic pyelonephritis with hypertension from essential hypertension with pyelonephritis. A cause of the hypertension was discovered in 48 of the 64 cases. Of the remaining 16 cases of essential hypertension only 5 were malignant. Essential malignant hypertension was not encountered in patients under the age of 34; young persons with the malignant type of hypertension are nearly always suffering from secondary hypertension, especially that due to pyelonephritis. It was thought probable that benign and malignant hypertension begin at about the same age; the ages at which they were encountered clinically in this series was 45·2 years for malignant hypertension and 53·2 years for benign hypertension. *S. Oram*

The Relationship of Chronic Alcoholism to Atherosclerosis. S. L. WILENS. *J. Amer. med. Ass.*, **135**, 1136–1139, Dec. 27, 1947.

This is a study of necropsy findings in 519 persons aged 35 or older, with chronic excessive alcoholism at Bellevue Hospital, New York, during the past 12 years. In approximately one-half of these addicts the daily consumption was known to have exceeded 1 pint (568 ml.) of whisky or its equivalent for many years. In all the others consumption was known to have been excessive for long periods of time. The incidence of atherosclerosis is compared with that in a control group of 600 consecutive necropsies of total abstainers and moderate consumers of alcohol, aged 35 or older. In the alcoholic group atherosclerosis was less common and less severe than in the control group, as also were lesions of the coronary and cerebral arteries. An explanation may be found in the fact that although three-fourths of the control group were 55 years or older at death, only one-half of the alcoholic men and one-fourth of the women survived beyond the age of 55. Of the alcoholics 28% had cirrhosis, but this did not increase the incidence of atherosclerosis. In age groups the incidence of atherosclerosis in the 423 alcoholic and 434 non-alcoholic men was almost identical. The author considers that the differences in incidence of atherosclerosis in the two groups depend not on alcoholism itself but on associated differences in age, blood pressure, and nutrition. Hypertension, diabetes, and obesity were all less common in the alcoholics. His conclusion is that substitution of alcohol for ordinary foods in the diet has no appreciable effect on the development of atherosclerosis.
Donald Hall